Ionic Liquids as Efficient Extractants for Quercetin from Red Onion (*Allium cepa L.)*

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Abstract: The solubility of Quercetin in alcohols, esters and in 1-ethyl-3-methylimidazolium trifluoroacetate, [EMIM][TFA] ionic liquid (IL) using the dynamic method was measured at constant pH in a range of temperature 233-373 K and compare to the literature data. The experimental solubility data have been correlated by means of commonly known G^E models,UNIQUAC and NRTL with the assumption that the systems studied here present simple eutectic behaviour. The basic thermal properties of Quercetin, i.e., fusion temperature and the enthalpy of fusion have been measured with differential scanning microcalorimetry technique (DSC).The application of alcohols, esters and ionic liquids (ILs) as alternatives to conventional organic solvents in the liquid-liquid extraction of Quercetin from different medicinal plants, flowers and frozen red onion (*Allium cepa L.*) was investigated. The parameters affecting the extraction yield using ILs such as chemical structures of the IL cation and anion, the phase volume ratio of extracting solvent, time of extraction and the Quercetin form of sample and concentration were evaluated. Specific Quercetin composition was performed through HPLC measurements. Using the most effective ILs in extraction, the 14.3±0.1g·kg^{-1} and 5.9±0.1 g·kg^{-1}of Quercetin from frozen pure red onion was obtained with *N*,*N*-diethyl-*N*-methyl-*N*-(2-methoxyethyl)ammonium tetrafluoroborate, [$N_{2,2,1,2OCH3}$][BF_4] and 1-ethyl-3-methylimidazolium trifluoroacetate, [EMIM][TFA], respectively.

Keywords: Quercetin, Ionic liquids, Solubility, Extraction from red onion, Hydrogen bonding interaction.

1. INTRODUCTION

Red onion was one of the first cultivated crops due to their long storage and portability. It could be dried and preserved for several months. Red onion was revered to possess anti-bacterial and anti-fungal activities and contains the powerful antioxidants, sulfur and other numerous phenolic compounds which arouse great interests. Although onion has been used for centuries in herbal and traditional medicine, it is only the last twenty years that some of the laboratories have interested in the extraction of flavonoids from red onion. Quercetin, a flavonoid of the secondary plant polyphenolics with significant antioxidant and chelating properties, containing five phenol functional groups, is a kind of amphoteric compound (Figure **1**) found in fruits, vegetables, wines, teas, plants and in the lignin fraction of lignocellulosic raw materials [1-3]. Therefore, Quercetin is an integral part of the human diet. In food technology Quercetin is used to preserve food and in an industry to prevent deterioration of rubbers and plastics. Few hydroxyl groups confirm the substantial antioxidant, chelating and prooxidant activity of the molecule. A double bond and carbonyl function increase their activity by affording a more stable Quercetin radical through conjugation and electron delocalization. Quercetin has a wide range of biological actions including anti-carcinogenic, anti-inflammatory and antiviral activities; as well as attenuating lipid peroxidation, platelet aggregation and capillary permeability [4]. Quercetin has demonstrated unique cardioprotective effects [3].

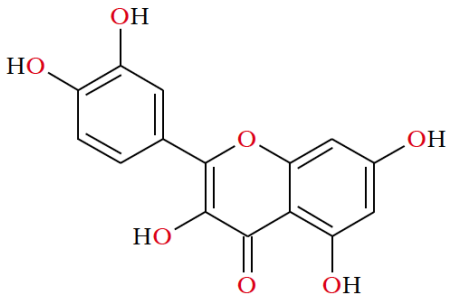

Figure 1: Chemical structure of Quercetin.

Extracts of flavonoids from herbs, vegetables or plants are of increasing interest in the food and pharmacy industry. Flavonoids retard oxidative degradation of lipids and thereby improved the quality and nutritional value of food. Quercetin has been found to inhibit xanthine oxidase activity, resulting in a decrease in oxidative injury [5]. Two-month (Quercetin + vitamin C) supplementation in nonprofessional athletics with regular exercise was effected in

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reducingoxidative stress and reducing inflammatory biomarkers [6]. Quercetin reveals strong antimicrobial activity and the sulfonic Morin derivative of Quercetin have shown detoxification activity against mercury, cadmium and lead in rats [7-9].

The extraction of Quercetin from natural resources usually involves the use of liquid-liquid extraction which adopts conventional organic solvents such as mixture (methanol/water, 75:15) or *n*-hexane from Guava Leaves (*Psidium guajava*) [10], ethanol-water from red onion [11], with toluene, dichloromethane and ethanol from red onion (partitioned with diethyl ether, ethyl acetate, or 1-butanol) [12], or ethyl acetate from red onion [8], or with ILs from Guava Leaves (*Psidium guajava*), or *Smilax china* tubers [13]. In this work mainly Imidazolium–based ILs and one Pyridinium-based IL were used with Chloride, Bromide, Dicyanamide, and Dihydrogenphosphate anions [13]. Optimized extraction of bioactive compounds including Quercetin from *Herba Artemisiae Scopariae* with ionic liquids and deep eutectic solvents as co-solvents with water-methanol solvent was recently published [14]. The best results were obtained with, 1-butyl-3-methylimidazolium bromide, [BMIM][Br] (899.73 μg/g of Quercetin) [14].

Ionic liquids (ILs) have received a lot of interest recently as the new solvents for extraction processes as well as the reaction media because of the unusual properties of ILs such as a high thermal stability, non-volatility, non-flammability and high solvation properties [15-19]. Additionally, the design ability of ILs makes them attractive alternatives to the popular, conventional organic solvents. Interesting review on biological activities of ILs with a special attention on their potential use in pharmaceutics and medicine was recently presented [20].

The conventional solvents are volatile, irritant, and flammable. Therefore, it is a hot spot to find environmentally benign solvents to replace the conventional solvents in the extraction process of alkaloids, or in general bioactive compounds [13,21-24]. In the last two decades, several new works reported the use of ILs as extractants for the extraction of small organic extractable compounds from biomass, lipids, and other hydrophobic compounds, proteins, amino acids, nucleic acids, and pharmaceuticals. ILs have been studied as solvents, co-solvents, co-surfactants, electrolytes, and adjuvants, as well as used in the creation of IL-pharmaceutical materials for better solubility. The IL-based processes are proposed as solid-liquid or liquid-liquid extractions, IL-modified materials, and IL-based crystallization approaches for the separation performance [24]. However, the use of ILs may be more expensive not only of its price but also because another process has to be designed to extract the solute from IL using a conventional organic solvent. The best way is to use only small amount of the IL as co-solvent with water, or organic solvent. An additional problem is the toxicity of the ILs in comparison with ethanol, for example.

Ethanol is used as a popular solvent in the supercritical CO_2 extraction of flavonoids. The effects of extraction time, temperature, pressure and different concentration of ethanol and their interactions on the yields of extraction of Quercetin from onion skins, different plants and green tea by supercritical CO_2 was investigated intensively during the last years [25-29].

The extraction of flavonoids from different plants strongly depends on their solubility in chosen traditional organic solvents or ILs. The solubility of Quercetin was measured in (water + methanol) and (water + ethanol) mixtures using UV-vis spectrophotometric method [30] and was calculated by linear free energy equations in water and in (water + ethanol) mixtures [31]. The solubility in mole fraction is on the level of 5.51×10^{-5} in water, 91.90×10^{-5} in methanol and 153×10^{-5} in ethanol at temperature 298.55 K [30]. The solubilization of Quercetin in copolymer ethylene oxide-propylene oxide in the presence of additives (Glucose, Glycine, Sodium Chloride, Urea, and Ethanol) was measured using a UV-vis spectrophotometric method [32]. The positive effect was observed for glucose, glycine and sodium chloride. The solubility in two ILs, such as 1-butyl-3-methylimidazolium trifluoromethanesulfonate, [BMIM][OTf] and in 1-butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide, [BMIM][NTf_2] was also presented [33]. The solubility in ILs was much larger than those in conventional organic solvents; in [BMIM][OTf] was on the on the level of 0.0109 in mole fraction at temperature 294.35 K.

The information about biodegradability and biotoxicity has been growing extensively but still need attention. Between different ILs, the most popular for pharmaceutical applications and drug delivery systems are ammonium-based ILs [34-36]. The ammonium-based ILs, hydrophobic, air and moisture stable compounds are multifunctional organic salts that are used both in industrial processes [17,34,37], catalytic reactions [38,39], as antibacterial, anti-fungal agents, and anti-electrostatic agents [34,40]. Ammonium-based

ILs are not expensive and are used also as cationic surfactants, biocides, and germicides [41].

The most often used is choline chloride, the *N*,*N*,*N*-trimethyl-hydroxyethyl-ammonium chloride, $[N_{1,1,1,2OH}][Cl]$ salt, non-toxic, and biodegradable since it is naturally occurring in several biological functions. The data on choline chloride derivatives physicochemical properties and solubility in alcohols, water, ethers, and many others solvents were presented in the open literature [42-45]. Choline-based ILs are known as less toxic and better biodegradable ILs in comparison to popular imidazolium-, or pyridinium-based ILs [46,47].

The goal of this work is to show better solubility of Quercetin in the IL than in popular organic solvents, thus the DSC of Quercetin was measured and the correlation of the solubility in different solvents was presented in comparison with the literature data. The solubility of Quercetin was measured in the most popular organic solvents such as 1-propanol, 1-butanol, ethyl acetate, butyl acetate and in the IL soluble in water, such as 1-ethyl-3-methylimidazolium trifluoroacetate, [EMIM][TFA]. Than, the extraction of Quercetin from different plants, from different forms of red onion and from an aqueous or organic phase of red onion using a series of solvents and hydrophobic or hydrophilic ILs was shown to check their extraction ability for Quercetin. The phase volume ratio of IL/water, the alkane length substituent at the cation of the IL, the time and the temperature of the extraction were optimized. The relationship between the IL structure and the extraction yield was studied and discussed. Parameters affecting the extraction efficiency were optimized and the best extracting ILs were presented for the chosen method of the extraction.

2. MATERIALS AND METHODS

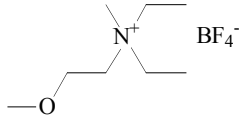
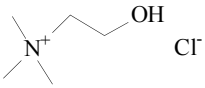
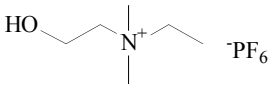
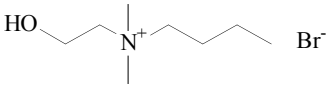
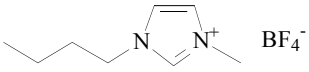
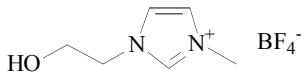
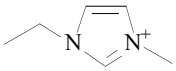
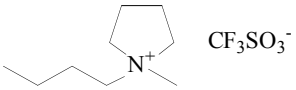
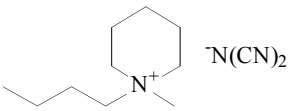
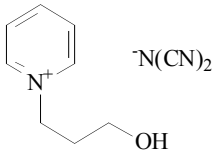
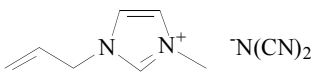
2.1. Materials

Quercetin was delivered from Sigma-Aldrich, Germany, CAS 117-39-5, ≥ 95% (HPLC). The structure is presented in Figure **1**. Solvents were purchased from Sigma-Aldrich and other companies as is listed in Table **1**. The freshly activated molecular sieves of type 4Å (Union Carbide) were used for drying solvents. A complete list of the investigated in this work ILs miscible with water and immiscible with water, along with their suppliers, CAS numbers, purity, and purification/analysis methods are summarized in

Table 1: Summary of chemical sample information for the investigated Quercetin and solvents: supplier, mass fraction purity, water content, purification method, analysis method and CAS No

Compound	Supplier	Mass fraction purity/ watercontent (mass fraction)	Purification method	Analysis Method	CAS Number, *M*/ g mol^{-1}
Quercetin	Sigma-Aldrich	0.95			117-39-5/ 302.24
Methanol	Sigma-Aldrich	for HPLC 0.999/30x10^{-6}	Molecular Sieves	GC	67-56-1/ 32.04
Ethanol	Sigma-Aldrich	0.995/120 x10^{-6}	Molecular Sieves	GC	64-17-5/46.07
1-Propanol	POCH	0.99/90 x10^{-6}	Molecular Sieves	GC	71-23-8/ 60.10
1-Butanol	POCH	0.99/80x10^{-6}	Molecular Sieves	GC	71-36-3 74.12
Ethyl acetate	CHEMPUR	0.995/120x10^{-6}	Molecular Sieves	GC	141-78-6 88.11
Butyl acetate	Sigma-Aldrich	0.99/130x10^{-6}	Molecular Sieves	GC	123-86-4 116.16
Acetonitrile	Sigma-Aldrich	for HPLC 0.999/30x10^{-6}		GC	75-05-8 41.05
Trifluoroacetic acid	Sigma-Aldrich	0.99/60x10^{-6}		GC	76-05-1 114.02

Table 2: Properties of the investigated ionic liquids, miscible with water: structure, name, abbreviation of name, supplier, CAS No., molar mass (*M*), mass fraction purity and water content

Structure	Name, abbreviation, supplier, CAS no	M/ gmol^{-1}	Mass fraction purity/water content
	*N*,*N*-Diethyl-*N*-methyl-*N*-(2-methoxyethyl)ammonium tetrafluoroborate, $[N_{2,2,1,2OCH3}][BF_4]$, Io-Li-Tec, 464927-72-8	233.06	≥0.99/ 430x10^{-6}
	Choline chloride,$[N_{1,1,1,2OH}][Cl]$ Merck, 67-48-1	139.62	≥0.97/ 330x10^{-6}
	*N*-Ethyl-*N*-(hydroxyethyl)-*N*,*N*-Dimethylammonium hexafluorophosphate, $[N_{2,1,1,2OH}][PF_6]$, synthesized [48]	263.20	≥0.97/ 600x10^{-6}
	*N*-Butyl-*N*-(hydroxyethyl)-*N*,*N*-dimethylammonium bromide, $[N_{4,1,1,2OH}][Br]$, synthesized [48]	226.19	≥0.97/ 520x10^{-6}
	1-Butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF_4] Io-Li-Tec, 174501-65-6	226.02	≥0.99/ 540x10^{-6}
	1-(2-Hydroxyethyl)-3-methylimidazolium tetrafluoroborate, [EtOHMIM][BF_4] Io-Li-Tec, 374564-83-7	213.97	≥0.98/ 420x10^{-6}
	1-Ethyl-3-methylimidazolium trifluoroacetate,[EMIM][TFA] Sigma-Aldrich, 174899-65-1	224.18	≥0.97/ 320x10^{-6}
	1-Butyl-1-methylpyrrolidinium trifluoromethanesulfonate, [BMPYR][OTf] Io-Li-Tec, 367522-96-1	291.33	≥0.99/ 370x10^{-6}
	1-Butyl-1-methylpiperidinium dicyanamide,[BMPIP][DCA] Io-Li-Tec (custom synthesis)	222.38	≥0.97/ 420x10^{-6}
	*N*-(3-Hydroxypropyl)pyridinium dicyanamide, [*N*-C_3OHPY][DCA] synthesized [49]	204.26	≥0.95/ 456x10^{-6}
	1-Allyl-3-methylimidazolium dicyanamide,[AMIM][DCA] Io-Li-Tec, 917956-73-1	189.22	≥0.98/ 560x10^{-6}

Tables **2** and **3** [48-53]. ILs were purified before use during 24 h under low pressure, at temperature T = 368.15 K.

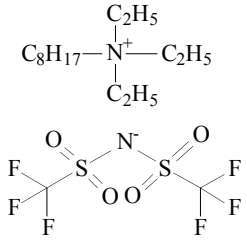
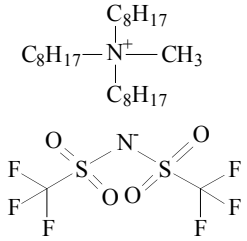
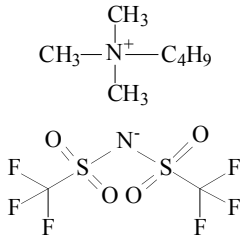
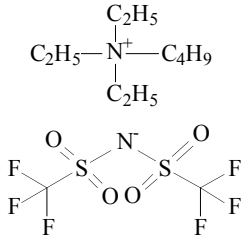
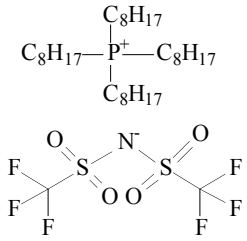
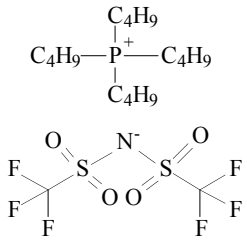
2.2. Water Content

The water content was analyzed by the Karl-Fischer titration technique (method TitroLine KF). The water contamination in all compounds (see Tables **2** and **3**) [43-52] was below 600ppm.

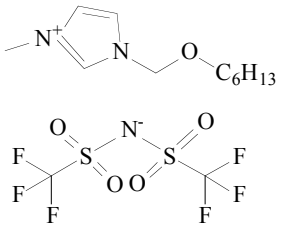
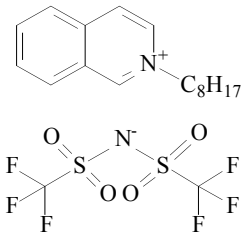
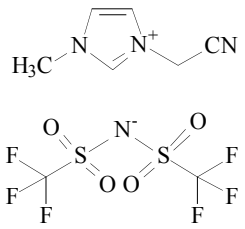
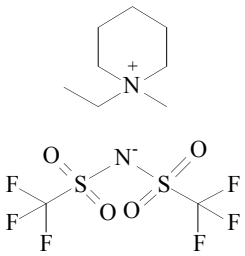
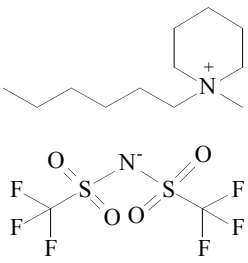
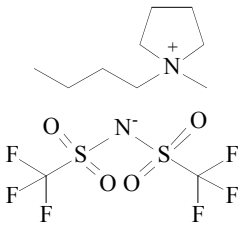
2.3. Differential Scanning Microcalorimetry, DSC

The temperature of fusion (T_{fus}) and enthalpy of fusion ($\Delta_{fus}H$) of Quercetin have been measured using a differential scanning microcalorimetry technique (DSC).

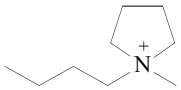
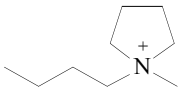
Table 3: Properties of the investigated ionic liquids immiscible with water: structure, name, abbreviation of name, supplier, CAS No., molar mass (*M*), mass fraction purity and water content

Structure	Name, abbreviation, supplier, CAS no	M/ g mol^{-1}	Mass fraction purity/water content
	*N*-Octyl-*N*-triethylammonium bis{(trifluoromethyl)sulfonyl}imide, [$N_{8,2,2,2}$][NTf_2], Io-Li-Tec, 210230-48-1	494.56	≥0.98/ 280x10^{-6}
	*N*-Methyl-*N*-trioctylammonium bis{(trifluoromethyl)sulfonyl}imide, [$N_{8,8,8,1}$][NTf_2], Io-Li-Tec, 375395-33-8	648.85	≥0.99/ 300x10^{-6}
	*N*-Butyl-*N*-trimethylammonium bis{(trifluoromethyl)sulfonyl}imide, [$N_{4,1,1,1}$][NTf_2], Io-Li-Tec, 258273-75-5	396.37	≥0.98/ 350x10^{-6}
	*N*-Butyl- *N*-triethylammonium bis{(trifluoromethyl)sulfonyl}imide, [$N_{4,2,2,2}$][NTf_2], Io-Li-Tec, 324574-91-6	438.45	≥0.99/ 420x10^{-6}
	Tetraoctylphosphonium bis{(trifluoromethyl)sulfonyl}imide,[$P_{8,8,8,8}$][NTf_2], synthesized [50]	764.0	≥0.98/ 460x10^{-6}
	Tetrabutylphosphonium bis{(trifluoromethyl)sulfonyl}imide, [$P_{4,4,4,4}$][NTf_2] Synthesized from [$P_{4,4,4,4}$][Br] , Sigma Aldrich ≥0.99	539.64	≥0.98/ 560x10^{-6}

(Table 3). Continued.

Structure	Name, abbreviation, supplier, CAS no	M/ g mol^{-1}	Mass fraction purity/water content
	1-Hexyloxymethyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide, [$C_6H_{13}OCH_2MIM$][NTf_2], synthesized [51]	477.49	≥0.97/ 420x10^{-6}
	*N*-octylisoquinolinium bis{(trifluoromethyl)sulfonyl}imide,[C_8iQuin][NTf_2], synthesized [52]	522.52	≥0.97/ 380x10^{-6}
	1-Cyanomethyl-3-methylimidazolium, bis{(trifluoromethyl)sulfonyl}imide,[ECNMIM][NTf_2], synthesized [53]	402.32	≥0.97/ 490x10^{-6}
	1-Ethyl-1-methylpiperidinium bis{(trifluoromethyl)sulfonyl}imide, [EMPIP][NTf_2], Io-Li-Tec (custom synthesis)	408.42	≥0.97/ 490x10^{-6}
	1-Hexyl-1-methylpiperidinium bis{(trifluoromethyl)sulfonyl}imide, [HMPIP][NTf_2], Io-Li-Tec,	464.54	≥0.99/ 360x10^{-6}
	1-Butyl-1-methylpyrrolidinium bis{(trifluoromethyl)sulfonyl}imide, [BMPYR][NTf_2], Io-Li-Tec, 223437-11-4	422.41	≥0.985/ 290x10^{-6}

(Table 3). Continued.

Structure	Name, abbreviation, supplier, CAS no	M/ g mol^{-1}	Mass fraction purity/water content
	1-Butyl-1-methylpyrrolidinium tricyanomethanide, [BMPYR][TCM] Io-Li-Tec, 878027-72-6	232.32	≥0.98/ 340x10^{-6}
	1-Butyl-1-methylpyrrolidinium tetracyanoborate, [BMPYR][TCB], Merck, 1266721-18-9	257.15	≥0.98/ 280x10^{-6}

The applied scan rate was 10 K·min^{-1}, with a power and recorder sensitivities of 16 mJ·s^{-1} and 5mV, respectively. The apparatus (DSC 1 STARe System from Mettler Toledo with Liquid Nitrogen Cooling System) was calibrated with a 0.999999 mol fraction purity indium sample. Temperature of the observed phase transition was determined from the second heating scan See Figure **1S** in the supplementary material. The uncertainty of the melting temperature was $u(T_{fus})$ = ± 0.3K (average over three scans). The uncertainty of the enthalpy of phase transition was $u(\Delta_{fus}H)$ = ± 1.4 kJ·mol^{-1}.

2.4. Solubility Apparatus and Measurements

A well-known dynamic (synthetic) method of the solubility measurements was used [54]. The sample of Quercetin was dissolved in previously dried with $MgSO_4$ acetone (Chempur, CAS:67-64-1). The cloudy solution was filtrated using 0.2μm syringe filters. Received filtrate was evaporated and purified Quercetin was dried in vacuum at temperature 315 K for two hours. Samples for solubility measurements of about 0.03g, prepared by weighing, were heated slowly (about 5 K·h^{-1}) with continuous stirring inside a Pyrex glass cell (volume of the cell was 10 ml) placed in a thermostated water bath. Temperatures of crystal disappearance were measured with an electronic thermometer P 550 (Dostmann Electronic GmbH, Germany) installed in the bath, and were detected visually with an increasing temperature. A heater was installed in the bath and heating rate was controlled with Laboratory Autotransformer AL-2500. The error did not exceed $u(x)$ = 0.0002 in mole fraction. The uncertainties of the temperature measurements were judged to be $u(T)$ = ± 0.2K.

2.5. Extraction from Different Plants/Samples

Ethanol (250-320ml) was used to extract Quercetin from 25g of different plants/samples of flowers in order to compare extraction efficiency from different materials with one organic solvent. Probes of plants, flowers, and tea were dry and were used as supplied. The water content was not measured. Ethanol is widely used for extraction of Quercetin and is a better solvent than water. An experiment was performed in Soxhlet apparatus during 10h at temperature T = 353.15 K. The product of extraction was dried during 6h in a vacuum after the removing of ethanol by distillation. The LaChrom (Merck Hitachi) HPLC system equipped with an L-7420 UV-VIS visible dual wavelength detector, four-solvents low-pressure gradient pomp type L-7100 was used for analysis of Quercetin. System was controlled by the HPLC System Manager Model D-7000 program.

2.6. Extraction from Red Onion in Different Forms

Ethanol (310-350cm^3) was used to extract Quercetin from 20-50g of raw or frozen red onion with skin in order to compare extraction efficiency from different samples and from different producers (onion 1 to onion 5). The experiment was performed in Soxhlet apparatus during 10h at temperature T = 353.15 K. Product of extraction was dried during 6h in a vacuum after the removing of ethanol by distillation. The analysis was made using HPLC system.

The choice of red onion instead of lovage is a result of our experiment. The extraction of Quercetin with ethanol from lovage is lower than that from frozen onion, especially from different producers. The probe of the onion was mixed with skin. The distribution of Quercetin in the red onion (skin versus internal) was not controlled. Freezing is keeping Quercetin for a longer time in the probe.

2.7. Extraction with Ethyl Acetate, Butyl Acetate and ILs Soluble in Water

The mixture of 0.5 g of the IL and 0.09g of the extract of frozen red onion 1, or 5, 1.0g of water and

1.5g of solvent (ethyl acetate or butyl acetate instead of ethanol to increase the extraction-the larger solubility of Quercetin was shown in esters) was mixed together under vigorous stirring (1250 rpm) for 24h, or 48h (or 72h for comparison). The mixture of these compounds was introduced into a jacketed glass cell with a volume of 10 cm^3. The temperature was controlled with a thermostatic water bath (LAUDA Alpha) to maintain a constant temperature of T = 296.15 ± 0.5 K. After getting the phase separation for the time of about 20h, two phases were separated and analyzed with HPLC. The pH of water probes after the experiment was in a wide range, from pH = 2 ($[N_{2,2,1,2OCH3}][BF_4]$), pH = 3.5 ($[N_{4,1,1,2OH}][Br]$,$[N_{1,1,1,2OH}][Cl]$), pH = 4 ([EMIM][TFA]) to pH = 6 ([AMIM][DCA]). For the comparison, the process of extraction was also performed with pure solvents (ethyl acetate or butyl acetate) with or without the IL. The concentration of Quercetin in both phases was determined by the aforementioned HPLC instrument: the 0.1g of organic or water phase was concentrated and next dissolved in a 0.5ml mixture of methanol-water (4:1 in mass). The separation column was Atlantis® T3 (4.6mm × 250mm, 5μm). The liquid mobile phase was a mixture of 0.05w% aqueous solution of trifluoroacetic acid (A) and acetonitrile (B) of changing in time concentration. The results for one chosen IL, $[N_{2,2,1,2OCH3}][BF_4]$ are listed in Table **1S** in the supplementary material as an example. Table **2S** in the supplementary material presents the influence of the amount of the ammonium-based IL ($[N_{2,2,1,2OCH3}][BF_4]$) in the aqueous phase on the extraction efficiency at T = 296.15±0.5 K after 72h. The ratio of concentration of Quercetin in ester/(IL + water) phase and the concentration of Quercetin in the solvent phase (butyl acetate) is described. For the further experiments, the proportion of IL:water (1:2 in mass) was taken. Table **3S** in the supplementary material presents the final results of the extraction with $[N_{2,2,1,2OCH3}][BF_4]$, taken as an example, after the evaporation of solvents (water and butyl acetate). The representative high-performance liquid chromatography profiles of Quercetin extract from different solvents and ILs are available on request.

2.8. Extraction with ILs Insoluble in Water

The extraction of Quercetin was provided at the same temperature T = 296.15±0.5 K. A mixture of 1.5 g of the IL and 0.09 g of the extract of frozen red onion 1, or 5, and 1.5 g of water was mixed under vigorous stirring (1250rpm) for 48h (or 72h for comparison) which was the time to achieve extraction equilibrium. After getting the phase separation for about 20h, two phases were separated and analyzed with HPLC. The pH of probes of water phase was 3-5. The concentration of Quercetin in both phases was determined by the aforementioned HPLC instrument: the 0.1 g of IL or water phase was concentrated and next mixed in 0.5 ml of mixture methanol-water (4:1 in mass). The special treatments were applied to the IL solid at room temperature, such as $[P_{4,4,4,4}][NTf_2]$ and $[EMPIP][NTf_2]$. Extraction was made from frozen red onion 5 with mixtures of (water + methylene chloride, CH_2CL_2) and IL at the same temperature T = 296.15±0.5 K during 48h. For the $[P_{4,4,4,4}][NTf_2]$ the 0.5954 g of CH_2CL_2 and for $[EMPIP][NTf_2]$ 0. 6076 g of CH_2CL_2 were added. The separation column was Atlantis® T3 (4.6mm × 250mm, 5μm). The liquid mobile phase was described above. The representative high-performance liquid chromatography profiles of Quercetin extract from different solvents and ILs are available on request.

3. RESULTS AND DISCUSSION

3.1. Solubility Measurements

From differential scanning calorimetry (DSC) data, (see Figure **1S** in the supplementary material), the temperature of fusion T_{fus} = 592.4±0.3 K and enthalpy of fusion $\Delta_{fus}H$ = 48.23±1.4 kJ·mol^{-1} of Quercetin was observed. The previous published data were T_{fus} = 587.8 K and enthalpy of fusion $\Delta_{fus}H$ = 51.08 kJ·mol^{-1} [33]. We also noticed the solid-solid phase transition observed earlier in (T_{tr} = 381.55 K with heat effect 4.88kJ·mol^{-1} [33]) at a lower temperature and with lower heat effect. A very small reflection on the thermograph line was observed at T_{tr} = 359.8±0.3 K with the very low heat $\Delta_{tr}H$ = 2.48 ±1.4 kJ·mol^{-1}.

The solid-liquid phase equilibria, SLE diagram results from different interactions between the Quercetin and the solvent and is very similar to published earlier solubility data of Quercetin [30-33]. The complete miscibility in the liquid phase as in simple eutectic mixtures is observed. It is typical for the polar solvents as water, or alcohols, or ILs capable to form hydrogen bonding with the solute. The solubility of Quercetin was in mole fraction on the level of 5.51x10^{-5} in water, 91.90x10^{-5} in methanol and 153x10^{-5} in ethanol at a temperature T = 298.6 K [30]. The solubility in two ILs, such as 1-butyl-3-methylimidazolium trifluoromethanesulfonate, [BMIM][OTf] and in 1-butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}imide, $[BMIM][NTf_2]$, measured with the same method as in this work, was

Table 4: Experimental solid-liquid equilibrium temperatures, *T*/(K) as a function of mole fraction, x_1 for binary systems {Quercetin (1) + solvent (2)}

x_1	*T*/(K)	x_1	*T*/(K)
1-Propanol			
0.0038	293.7	0.0059	319.7
0.0042	300.4	0.0065	325.4
0.0046	304.8	0.0070	328.5
0.0050	309.3	0.0078	332.8
0.0054	313.5		
1-Butanol			
0.0019	298.9	0.0031	323.2
0.0021	304.3	0.0033	327.6
0.0023	307.7	0.0035	331.0
0.0025	312.5	0.0036	333.0
0.0028	318.6	0.0039	336.9
Ethyl acetate			
0.0006	295.1	0.0011	324.0
0.0007	301.9	0.0012	329.0
0.0008	308.4	0.0015	340.4
0.0009	315.6		
Butyl acetate			
0.0005	298.6	0.0008	327.6
0.0006	309.5	0.0010	335.6
0.0007	320.0	0.0012	341.6
[EMIM][TFA]			
0.2289	291.4	0.3043	318.6
0.2387	294.9	0.3202	319.1
0.2442	298.2	0.3462	323.4
0.2499	300.3	0.3648	325.0
0.2568	304.9	0.3756	326.2
0.2647	308.0	0.3910	326.7
0.2759	312.6	0.3962	327.2
0.2899	315.2	0.4100	328.2

much larger [33]. The solubility in [BMIM][OTf] was on the level of 0.0109 in mole fraction at temperature T = 294.4 K. In this work, the solubility was measured in alcohols, esters and in IL, 1-ethyl-3-methylimidazolium trifluoroacetate, [EMIM][TFA]. The results of the solubility measurements are listed in Table **4**. The Table **4** includes the direct experimental results of the solubility temperatures, *T*/(K) versus Quercetin mole fraction, x_1. Results for conventional solvents are presented in Figure **2** together with the literature data [30]. The results show much better solubility of Quercetin in 1-propanol than in water, methanol, ethanol, and 1-butanol, which is on a level of 0.0042±0.0002 in mole fraction at temperature 300.15 K. The solubility in esters is lower than that in 1-butanol and 1-propanol and is on the level of 0.0007±0.0002 at a temperature of 301.9 K (ethyl acetate). Even the solubility of Quercetin in butyl acetate is slightly worse than that in ethyl acetate (in mole fraction), the biological experiments provided in this work revealed

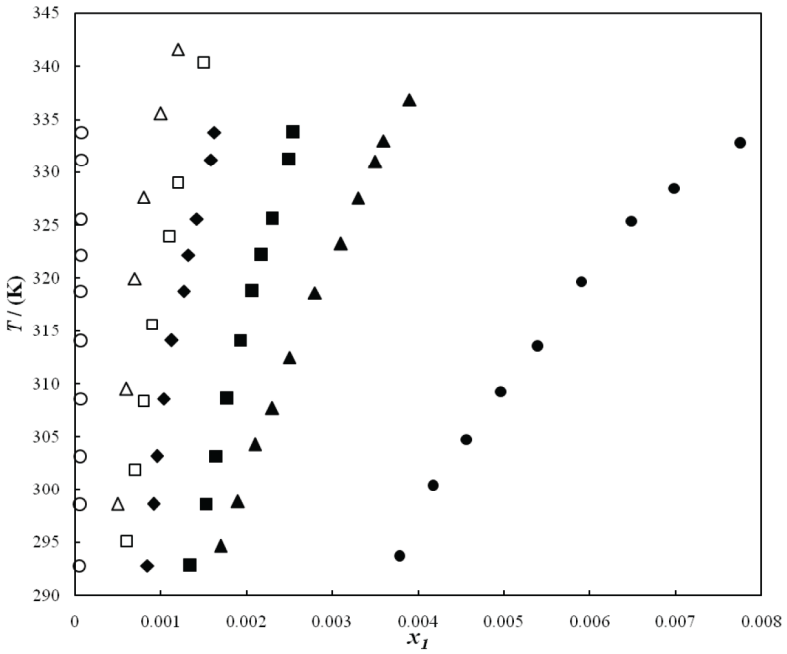


Figure 2: Solubility of Quercetin (1) in common solvents:○, water (2) [30]; ♦, methanol (2) [30]; ■, ethanol (2) [30]; ●,1-propanol (2); ▲, 1-butanol (2); □, ethyl acetate (2); ∆, butyl acetate (2).

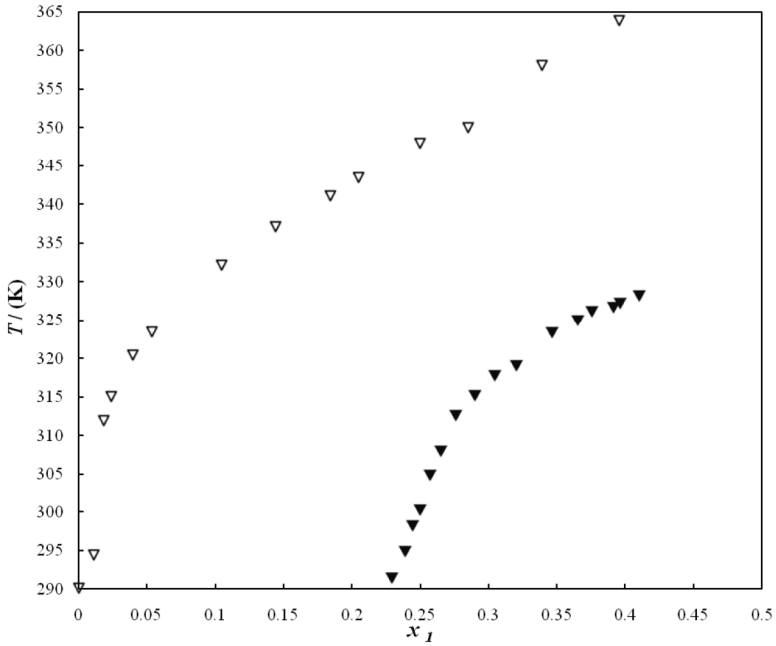


Figure 3: Solubility of Quercetin (1) in ionic liquids: ▲, [EMIM] [TFA] (2); △, [BMIM][OTf] [33].

the slightly better extraction with butyl acetate (in mass). Methanol was chosen as an extraction agent for Quercetin from *Herba Artemisiae Scopariae* as a better extraction solvent than water, ethanol, ethyl acetate and dichloromethane [14]. The solubility of Quercetin in the ILs is presented in Figure **3**. The solubility of Quercetin in [EMIM][TFA] is much higher (x_1 = 0.2442 ±0.0002 at temperature T = 298.15 K) than that in BMIM][OTf] [33]. We will present later that this IL will give good results in biological extraction. The results of SLE authorize us to assume that the measured binary systems present the simple eutectic systems with complete miscibility in the liquid phase.

Many phase equilibrium diagrams show that ILs with the short alkane chain length substituent at the cation (methyl- to butyl-) reveal a similar interaction with alcohol or water, thus mainly the anion entity is

favoured in the {IL + alcohol, or water} mixtures. Thus the extraction experiment from an ethanol/water extract of frozen red onion will be presented in this work with many different ILs of different anions.

3.2. Correlation of the Solubility Curves

The correlation of the experimental curves was made using the excess Gibbs energy (G^E) models: the UNIQUAC equation [55] and the NRTL equation [56].The equation frequently applied to the solubility data calculations is:

$$-\ln x_1 = \frac{\Delta_{fus}H_1}{R}\left(\frac{1}{T}-\frac{1}{T_{fus,1}}\right)+\frac{\Delta_{tr}H_1}{R}\left(\frac{1}{T}-\frac{1}{T_{tr,1}}\right) - \frac{\Delta_{fus}C_{p1}}{R}\left(\ln\frac{T}{T_{fus,1}}+\frac{T_{fus,1}}{T}-1\right)+\ln\gamma_1 \quad (1)$$

where x_1, γ_1, $\Delta_{fus}H_1$, $\Delta_{fus}C_{p1}$, $T_{fus,1}$, T, $\Delta_{tr}H_1$ and $T_{tr,1}$ are mole fraction, activity coefficient, enthalpy of fusion, difference in solute heat capacity between the liquid and solid phase at melting temperature, melting temperature, equilibrium temperature, enthalpy of the solid-solid phase transition and transition temperature, respectively. If a solid-solid phase transition occurs before fusion, the solubility equation for temperatures below that of the phase transition must include the effect of the transition. Calculations were made without the $\Delta_{fus}C_{p1}$ term because of lack of data. The activity coefficient is temperature as well as mole fraction dependent and can be calculated from equations expressing excess Gibbs energy (G^E) by using the Gibbs-Duhem equation. The applied equations have two adjustable parameters P_1 and P_2 (in NRTL equation the α parameter is fixed additionally for the best results of correlation), which are determined by minimization of the objective function F(P_1, P_2), defined as follows:

$$F(P_1,P_2)=\sum_{i=1}^{n}\left[T_{exp,i}-T_{calc,i}(x_i,P_1,P_2)\right]^2 \quad (2)$$

where n denotes the number of experimental points. As a measure of the reliability of the correlations, the root-mean-square deviations of temperature, RMSD, σ_T/(K), have been calculated according to the following equation:

$$\sigma_T=\left\{\sum_{i=1}^{n}\frac{\left(T_{exp,i}-T_{calc,i}\right)^2}{n-2}\right\}^{1/2} \quad (3)$$

The values of the parameters and the corresponding RMSDs of temperature, σ_T/(K), are listed in Table **4S** in the supplementary material. The average values of the root-mean-square deviations of temperature were σ_T = 1.42K and σ_T = 3.81K for UNIQUAC and NRTL, respectively. The solubility data was at much lower temperatures than the melting temperature, and the correlation was quite difficult and especially for a binary system with the IL using UNIQUAC model impossible.

3.3. Extraction Results

The red onion was selected as the best plant for the extraction of Quercetin after the examination experiment operated under the optimized conditions with ground lives of green tea and black Indian tea, *Epilobiumparviflorum*, pumpkin, dried mountain ash, lyophilized chokeberry, and dried lovage. The best results obtained from dried lovage with ethanol at temperature T = 353.15 K were on the level of 0.94w% (see Table **5**). The same results of the extraction of Quercetin from the different samples of red onion were much larger, on the level of 7.37w% to 48.47w% (probe 5). (See Table **1S** in the supplementary material).

The average value of three fresh samples of red onion was 11.4w%. In this experiment, the mean of the total mass of extracted Quercetin was from $2x10^{-5}$ g·kg^{-1} to 3.57 ± 0.04 g·kg^{-1} for different probes. The much better results were obtained for the same samples of red onion after the process of freezing (2h under temperature T = 253 K). The average value of the five frozen samples was 29.94w%. The mass of extracted Quercetin from different samples of red onion was from 8.14±0.05 g·kg^{-1} (red onion 4) to 41.0041.00±0.02 g·kg^{-1} (frozen red onion 1). Two, the best-frozen probes were taken for the further experimental procedure, 48.47w% and 33.02w% (See Table **1S**). Some of the literature data [12] and our parallel solubility data shows a possibility of using esters such as ethyl acetate or butyl acetate as a better extraction solvent than ethanol. After all, the ILs have strong dissolving power, thus they were employed as co-solvents and solvents in this work as well. From Table **2S** in the supplementary material, it can be seen that the addition of IL [$N_{2,2,1,2OCH3}$][BF_4] to the extraction solvent, ethyl acetate or butyl acetate at a temperature T = 296.1± 0.5 K after 48h obviously improved the extraction of Quercetin, especially with butyl acetate after 48h. The concentration of Quercetin in ethyl acetate/butyl acetate (without the IL) was 59.7/71.7w%

Table 5: Extraction of Quercetin (Q) from different amounts of plants/samples with about 300 cm^3 of ethanol at temperature *T* = 353.1±0.5 K during 4h-14h: the result product /(g), concentration of Quercetin in extract/(w%), and final concentration of Quercetin in kg of plant sample/($g \cdot kg^{-1}$)

Plant/sample	Amount of sample/(g)	Amount of ethanol/ (cm^3)	Extraction time/(h)	Product/(g)	Q in extract/ (w%)	Q in plant sample[a]/ ($g \cdot kg^{-1}$)
Ground green tea	17.07	320	12	4.18	0.23	0.56±0.05
Ground black Indian tea	23.2	270	14	4.92	0.30	0.64±0.05
Epilobium parviflorum	14.07	300	4	1.44	0.19	0.19±0.05
Pumpkin	25.01	300	10	1.10	0.06	0.00002±0.00002
Dried mountain ash	24.10	300	11	14.87	0.21	1.30±0.04
Chokeberry lypophilized	22.07	290	7.5	12.20	0.32	1.77±0.04
Dried lovage	10.02	300	11	3.81	0.94	3.57±0.04

[a]Mean ± SD of replicated samples.

after the addition of IL was 78.6/80.9w%. The concentration of Quercetin in the final product using butyl acetate after 24h is 1% better, but the ratio of Quercetin in ester phase/water phase is much better after 48h (14.8/1). These experimental results showed that the best organic solvent for the extraction procedure will be butyl acetate. Extraction of Quercetin from frozen sample 1 with (butyl acetate + IL, $[N_{2,2,1,2OCH3}][BF_4]$) at a temperature *T* = 296.1 ± 0.5 K after 48h with different ratio of IL/water shows that the best result is for 1/2 (14.8/1) with 80.9 w% of Quercetin in extract (see Table **3S**) and even 83.8 w% of Quercetin in extract after the evaporation of solvents and impurities (see Table **6**). In the best probe 0.0165g of yellow powder of 83.8w% concentration of Quercetin is 0.0138 g ±0.0005 of pure Quercetin. Thus in the used extract of frozen red onion 1 in mass m = 0.0927 g, 48.47w% of Quercetin was obtained, in mass 0.0449g ±0.0005 of pure Quercetin. The final yield of the extraction was (0.0138: 0.0449)x100%, which is 30.8w% (see Table **6**). In general, the addition of the IL increases the extraction yield. Time of the extraction, 24h or 48h does not make large changes in the extraction efficiency.

The equation of the extraction yield is:

$$Y = \frac{m_{extr} \cdot a}{m_0 \cdot b} 100\% \quad (4)$$

where m_{extr} is the mass of Q_{extr} after the evaporation of the solvent (g), *a* is the concentration of Q in extract (HPLC method) in %, m_0 is mass of the onion extract (g) and *b* is the concentration of Q in concentrated extract of onion (HPLC method) in % (48.47% frozen red onion 1 and 33.02 % frozen red onion 5).

To find out the optimal ILs and evaluate its performance in solvent extraction, ILs with different cations and anions were tested in this work. The structure of IL has a significant influence on the extraction results owing greatly to their dissolving ability. To facilitate the discussion of the relationship

Table 6: Extraction of Quercetin (Q) from frozen sample 1 with (butyl acetate + IL, $[N_{2,2,1,2OCH3}][BF_4]$) at temperature *T* = 296.1±0.5 K after 48h with different amounts of the IL after evaporation of solvents: Q in butyl acetate phase/(w%), mass of this phase/(g), mass of extract after evaporation/ (g) and final concentration of Q in butyl acetate phase /(w%)

Q in butyl acetate phase/(w%)	Mass of butyl acetate phase/ (g)	Mass of extract after evaporation/ (g)	Q in final extract[a]/ (w%)
84.2	1.1993	0.0055	86.4±0.2
80.9	1.1005	0.0165	83.8±0.2
76.0	1.2285	0.0075	79.3±0.2
81.9[b]	1.2692	0.0098	82.5±0.2

[a]Mean ± SD of replicated samples.
[b]Extraction after 24h for comparison.

between the chemical structures of ILs and their extraction ability, the ILs were divided into two groups: (1) ILs soluble in water (see Table **2**) and(II) ILs insoluble in water (see Table **3**).

The extraction of Quercetin from frozen sample 1 with binary mixture (butyl acetate + IL) at temperature T = 296.1 ± 0.5 K after 48h is shown in Table **7**. As can be seen, some interesting results may be obtained in terms of the influence of the IL cation structure. For the ammonium-based ILs with different anions, the extraction ability is higher than those for imidazolium-based, or piperidinium-based ILs. The large final concentration of Quercetin in butyl acetate phase/(w%) was obtained for $[N_{4,1,1,2OH}][Br]$, for which the extraction of Quercetin was larger than 80 w% in butyl acetate phase. Actually, all ILs soluble in water revealed extraction > 70 w%, except $[N_{2,1,1,2OH}][PF_6]$, for which the extraction ability was > 50w%. The analysis after the shorter time, 24h shows more Quercetin in the solvent phase and better extraction. In this case, the extension of time of extraction is not beneficial for the extraction process. The large concentration of Quercetin in the solvent phase (butyl acetate) was also observed for $[N_{1,1,1,2OH}][Cl]$, 27.41 from 0.5020 g of the IL. The probe with $[BMIM][BF_4]$ was unsuccessful because three phases were observed. Quercetin was observed in two phases (H_2O + IL). The sample of [*N*-C_3OHPY][DCA] was prepared from an extract of frozen red onion 5 (Q = 33.02w%). The results were similar to those in the other ILs (Quercetin in the solvent phase >70w%). The larger amount of impurities was observed in the solvent phase, 7.18w%.

After the next purification by the evaporation of butyl acetate and impurities the highest final concentration of Quercetin was observed for [EMIM][TFA] (79,9w%), $[N_{2,2,1,2OCH3}][BF_4]$ (80.9w%) and $[N_{4,1,1,2OH}][Br]$ (81.5w%) (see Table **7**). The most favourable salt for the extraction of these tree ILs is $[N_{4,1,1,2OH}][Br]$ because of the interaction with water, toxicity, and price. The probe has given 0.0171 g of yellow, solid phase with 80.1w % of Quercetin which means 0.0138±0.0005 g of pure Quercetin from final extract.

Interesting result was also obtained for [EMIM][TFA] (see Table 8). After purification, the 0.0056 g of extract was obtained in a form of yellow powder with a concentration of 85.53 w% of Quercetin from final extract. It is 0.0048 g of pure Quercetin. In 0.0780g of an extract of frozen red onion 1 (48.47w% of Quercetin) was 0.0378±0.0005 g of pure Quercetin. The final yield of the extraction was (0.0048/0.0378)x100% = 12.66%.The strong interaction between the imidazolium-based IL and Quercetin, especially by hydrogen bonding, π-π, and *n*-π interaction contributing greatly to this extraction.

Table **9** presents extraction of Quercetin mainly from frozen sample 1 with different ILs, insoluble in

Table 7: Extraction of Quercetin (Q) from frozen sample 1 with mixture (butyl acetate + IL miscible in water) at temperature T = 296.1±0.5 K after 48h: mass of IL and water/ (g),), mass of ethanol extract of Q and butyl acetate/(g), ratio of Q in butyl acetate phase to (H_2O + IL) phase and final concentration of Q in butyl acetate phase /(w%)

IL	IL/(g)	H_2O/(g)	Extract of onion/(g)	Butyl acetale/(g)	Q butyl acetate/Q (H_2O+ IL)	Q in butyl acetate[a]/(w%)
$[N_{2,2,1,2OCH3}][BF_4]$	0.5012	0.9964	0.0927	1.5027	14.8	80.9±0.2
$[N_{1,1,1,2OH}][Cl]$	0.5020	1.0008	0.0926	1.4966	27.41	74.3±0.2
$[N_{2,1,1,2OH}][PF_6]$	0.5014	1.0281	0.0927	1.5183	6.9	52.4±0.2
$[N_{4,1,1,2OH}][Br]$	0.5170	0.9862	0.0941	1.5086	0.8	81.5±0.2
$[BMIM][BF_4]$[b]	0.5012	1.0086	0.0932	1.5011	-	76.9±0.2
$[EtOHMIM][BF_4]$	0.5001	1.0521	0.0910	1.4843	25.21	70.2±0.2
[EMIM][TFA]	0.4348	0.8679	0.0780	1.3082	7.31	79.9±0.2
$[BMPYR][CF_3SO_3]$[b]	0.5090	1.0125	0.0929	1.5037	-	79.0±0.2
[BMPIP][DCA]	0.5032	1.000	0.10031	1.5648	2.99	77.2±0.2
[*N*-C_3OHPY][DCA][c]	0.5009	1.0026	0.10028	1.4992	4.89	74.0±0.2
[AMIM][DCA]	0.4987	0.9862	0.0877	1.4872	2.99	79.8±0.2

[a]Mean ± SD of replicated samples.
[b]Phase (H_2O+ IL) is in two parts. Q is in the (H_2O+ IL) phases.
[c]Extract of frozen red onion 5 (Q = 33.02 w%). Impurities in solvent's phase 7.18 w%.

Table 8: Extraction of Quercetin (Q) from frozen sample 1 with (butyl acetate + IL) at temperature *T* = 296.1±0.5 K after 48 h after the evaporation of solvents: Q in butyl acetate phase/(w%), mass of this phase/(g), mass of extract after evaporation/ (g) and final concentration of Q in butyl acetate phase /(w%)

IL	Q in butyl acetate phase/(w%)	Mass of butyl acetate phase/(g)	Mass of extract after evaporation/(g)	Q in final extract[a]/(w%)
$[N_{2,2,1,2OCH3}][BF_4]$	80.9	1.1005	0.0165	83.8±0.2
$[N_{1,1,1,2OH}][Cl]$	74.3	0.9715	0.0057	80.2±0.2
$[N_{4,1,1,2OH}][Br]$	81.5	1.154	0.005	78.6±0.2
[EMIM][TFA]	79.9	1.004	0.0056	85.5±0.2
[AMIM][DCA]	79.8	1.0766	0.0046	72.1±0.2

[a]Mean ± SD of replicated samples.

Table 9: Extraction of Quercetin (Q) from frozen sample 1, or 5 with different ILs insoluble in water at temperature *T* = 296.1±0.5 K after 48h (or 72h): mass of IL and water/ (g),),mass of ethanol extract of Q, ratio of Q in the IL phase and water phase and final concentration of Q in the IL phase /(w%)

IL	IL/ (g)	H_2O/ (g)	Extract of onion/ (g)	Q IL/Q H_2O	Q in IL/ (w%)
$[N_{8,2,2,2}]$ $[NTf_2]$[a]	1.5227	1.5056	0.0911	5.1	85.9±0.2
$[N_{8,8,8,1}]$ $[NTf_2]$[a]	1.5227	1.5070	0.0917	11.3	85.4±0.2
$[N_{4,1,1,1}]$ $[NTf_2]$[a]	1.5090	1.5242	0.0907	1.0	52.6±0.2
$[N_{4,2,2,2}]$ $[NTf_2]$[a]	1.5140	1.5140	0.0892	5.1	74.1±0.2
$[P_{8,8,8,8}]$ $[NTf_2]$	1.5030	1.5013	0.0904	7.3	67.0±0.2
$[P_{4,4,4,4}]$ $[NTf_2]$[b]	0.9008	1.4996	0.0997	4.0	76.6±0.2
$[C_6H_{13}OCH_2MIM][NTf_2]$[c]	1.4996	1.5032	0.0925	4.1	77.5±0.2
$[C_8iQuin]$ $][NTf_2]$[d]	1.5084	1.5025	0.1003	8.7	74.8±0.2
[ECNMIM][NTf_2][a,e]	1.5023	1.5002	0.0914	1.5	50.6±0.2
[HMPIP][NTf_2][d]	1.4924	1.5017	0.1005	2.45	74.6±0.2
[EMPIP][NTf_2][a,f]	0.9007	1.5112	0.1097	3.8	66.7±0.2
[BMPYR][NTf_2][g]	1.5019	1.4995	0.0895	3.13	71.5±0.2
[BMPYR][TCM][a,g]	1.5113	1.4973	0.0901	0.01	0.35±0.02
[BMPYR][TCB][h]	1.9031	1.8755	0.1123	212.6	56.5±0.2

[a]Extraction after 72 h.
[b]In 0.5954 g CH_2Cl_2; extract from frozen red onion 5.
[c]The 14.0 w% in an aqueous phase.
[d]Extract from frozen red onion 5.
[e]Probe unsuccessful; Q in organic phase /water phase, 1.5:1.
[f]In 0.6076 g CH_2Cl_2; extract from frozen red onion 5.
[g]Probe unsuccessful; Q in water phase.
[h]Probe unsuccessful; difficulties with the separation of phases; impurities in the IL phase.

water at temperature *T* = 296.1± 0.5 K after 72h. The results of the extraction are not so attractive as for ILs from group I. The concentration of Quercetin in extracting solvent (here IL) is much lower than those in solvent/ILs from group I. The values are from 1 ($[N_{4,1,1,1}][NTf_2]$) to 11.3 ($[N_{8,8,8,1}][NTf_2]$). The final concentration of Quercetin in the IL phase was observed from 50.6 w% ([ECNMIM][NTf_2]) to 85.9 w% ($[N_{8,2,2,2}][NTf_2]$). Some probes were unsuccessful for different reasons, such as difficult separation of phases ($[P_{8,8,8,8}][NTf_2]$, [BMPYR][TCB]) or large amount of Quercetin remaining in the water phase ($[C_6H_{13}OCH_2MIM][NTf_2]$, $[C_8iQuin][NTf_2]$, [ECNMIM][NTf_2], [HMPIP][NTf_2], [BMPYR][NTf_2]).

From the obtained results, the possibility of comparison of different cations for the same anion, bis{(trifluoromethyl)sulfonyl}imide is possible. Generally, hydrophobic interaction, hydrogen-bonding interaction and the steric hindrance are the key parameters affecting the extraction ability of ILs [57]. Usually, the increase of the alkyl chain length of the IL

cation hinders the interaction between ILs and extracting polar substance, decreasing the extraction ability. In our case, the steric hindrance effect of the alkyl chain in interaction with big size aromatic groups of Quercetin has the influence on the solubility of ammonium-based ILs in water. The lower solubility is always observed in the longer alkane chain-IL and at the same time the better extraction from the aqueous phase [58]. The better results of extraction are noticeable for three octyl-chains at cation, $[N_{8,8,8,1}][NTf_2]$ in comparison with $[N_{8,2,2,2}][NTf_2]$, $[N_{4,1,1,1}][NTf_2]$ and $[N_{4,2,2,2}][NTf_2]$ (see the results in Table **9**). The hydrophobicity of ILs increases with an increase in the alkyl chain length at the IL cation. The comparison of three 1-butyl-3-methylimidazolium-based ILs with different anions $[NTf_2]^-$, $[TCM]^-$ and $[TCB]^-$ have shown better results for more hydrophobic anion $[NTf_2]^-$. Two other ILs are not suitable for this extraction.

Two ILs were solid at temperature T = 296.1 K, thus the addition of methylene chloride to the mixture of (water + IL) was provided to increase the solubility. The results for $[P_{4,4,4,4}][NTf_2]$ and $[EMPIP][NTf_2]$ after 48h from an extract of frozen red onion 5 are presented in Table **9**. The extraction suitability was on the level of 76.6 w% and 66,7 w% for $[P_{4,4,4,4}][NTf_2]$ and $[EMPIP][NTf_2]$, respectively.

According to Table **7**, it can be seen that the addition of IL to the extraction solvent obviously improved the extraction ability of Quercetin, especially with $[N_{2,2,1,2OCH3}][BF_4]$, $[N_{4,1,1,2OH}][Br]$, $[N_{4,1,1,2OH}][Cl]$ and [EMIM][TFA] comparing to the extraction using butyl acetate (see Table **3S** in the SM). These conclusions have been indicated by the similar results of Quercetin extraction from the aqueous phase of *P. guajava* leaves with microwave method at higher temperature [13]. In that work, the addition of IL, soluble in water, increased the yield of extraction 2-5 times. The best results were obtained with 1-butyl-3-methylimidazolium phosphonate, $[BMIM][H_2PO_4]$ and 1-butyl-3-methylimidazolium bromide, [BMIM][Br] on the level of 74.5 w% and 69.5 w% [13]. The only comparison with ILs used in this work may be made for $[BMIM][BF_4]$ (here 76.9 w% to 59.5w% [13]). The [BMIM][Br] IL was chosen as the best extrahent for Quercetin from *Herba Artemisiae Scopariae* [14]. The $[DCA]^-$ based ILs were on the average level in both works. In our work the best results were noticed for [EMIM][TFA] (85.5w%), or $[N_{2,2,1,2OCH3}][BF_4]$ (83.8w%) or $[N_{4,1,1,2OH}][Br]$ (78.6w%). As is widely known the $[BF_4]$- based ILs are not popular for the technological use because of the possible fluoric acid formation in contact with water. Thus we presented this IL only from the scientific point of view but not for the further technological projects. The $[BMIM][BF_4]$ IL has shown also a large extraction efficiency for Quercetin in work [14].

The extraction efficiency increases with an increase in the phase volume ratio of IL/water. Finally, the IL/water ratio equating 1/2 was used in all our experiments. The final yield of extraction of Quercetin from red anion with ethanol/water/butyl acetate probes is shown in Figure **4**. To overlook the $[N_{2,2,1,2OCH3}][BF_4]$ (the final yield of the extraction 30.78%) and the [EMIM][TFA] (the final yield of the extraction 12.66%) were the best extrahents, better than choline chloride,$[N_{4,1,1,2OH}][Cl]$ (the final yield of extraction 10.18%). This suggests that besides hydrophobic interaction, there must have been other driving forces. As mentioned above, hydrogen-bonding interaction is an important parameter affecting the extraction ability of ILs. As can be noticed from Figure **4**, the hydrogen-bonding ability of $[N_{4,1,1,2OH}][Cl]$ with a hydroxyl group in cation is slightly weaker than that of [EMIM][TFA]. The interaction between cation and anion in $[N_{4,1,1,2OH}][Cl]$ is stronger and the extraction ability for Quercetin is lower. Another interesting phenomenon, which can be seen from Figure **4**, is that the extraction ability of $[N_{2,2,1,2OCH3}][BF_4]$ is much higher than that of former ILs due to its stronger hydrogen-bonding ability. This suggests that hydrogen-bonding interaction and hydrophobicity should be considered simultaneously when explaining the affinity between ILs and Quercetin in aqueous solutions.

It is also outstanding that the time increase not imposes noticeable increasing of the extraction when the IL concentration is constant. Larger extraction of miscible with water ILs may be related to the greater capacity of the IL to establish hydrogen bonds with the water molecules and Quercetin molecules. Aqueous phase goes to the detriment of the water molecules solvating the Quercetin, which endsup in the better extraction. Only for few ILs, the larger extraction yield is observed in the (IL + water) phase than in the butyl acetate phase. In the context of the anions of ILs in groups I and II, the yield of extraction of Quercetin decreases in the order: $[BF_4]^- > [TFA]^- > [Cl]^- > [Br]^- > [NTf_2]^- > [PF_6]^- > [DCA]^- > [TCM]^-$. Overall, ILs have potential applications as extraction solvents or additives to organic solvents for the extraction of Quercetin from red onion. The most effective ILs in extraction of Quercetin from the frozen red onion (sample 1) were $[N_{2,2,1,2OCH3}][BF_4]$ (14.3±0.1 $g \cdot kg^{-1}$), [EMIM][TFA] (5.9 $g \cdot kg^{-1}$), $[N_{1,1,1,2OH}][Cl]$ (4.7±0.1 $g \cdot kg^{-1}$) and [AMIM][DCA] (3.6±0.1 $g \cdot kg^{-1}$).

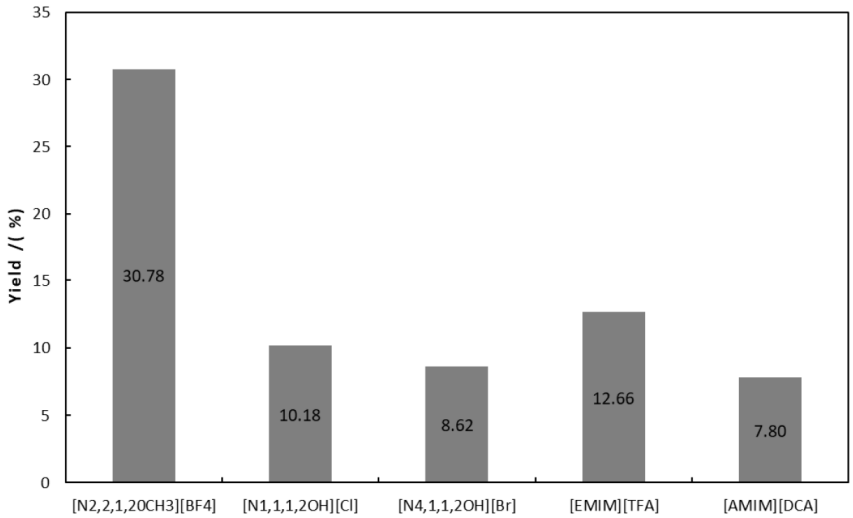


Figure 4: The final yield of extraction of Quercetin from red anion ethanol/water/butyl acetate probes.

The recovery of Quercetin from the IL phase and the recycling of the IL phase can be realized by using the evaporation of the solvent (for the ILs soluble in water) or crystallization effect (for the ILs insoluble in water).

4. CONCLUSION

Phase equilibrium data, the solubility of Quercetin in alcohols, or esters, or IL has been measured. The results were compared to literature data of alcohols and ILs. A comparison of the solubility of Quercetin in different solvents indicated the best extraction of Quercetin with high selectivity using [EMIM][TFA]. The simple eutectic mixtures with complete miscibility at liquid phase were observed in a wide range of mole fractions of the solvent. The correlation of the SLE data was undertaken with a commonly known G^E equations, the UNIQUAC and NRTL. The results of the correlation of SLE were satisfactory for all data with an average RMSD of temperature σ_T< 2.6 K.

In this work, the extraction of Quercetin from red onion by ethanol, ethyl acetate, butyl acetate, and 25 ILs with different hydrophobicity was conducted. It was found that the ability of extraction is dependent on the chemical structures of the IL cation and anion, on the phase volume ratio of extracted solvent and on the form of the sample of red onion. The more efficient extraction from water phase was obtained using the ILs soluble in water. Furthermore, the hydrophobic interaction between ILs insoluble in water and Quercetin is predominant due to their lower hydrophobicity and it increases with increasing of the IL cation alkyl chain length, enhancing the extraction ability of ILs used. For the ammonium-based ILs, an increase in the IL cation alkyl chain length results in the increase in the extraction ability of the IL. The more efficient extraction is obtained with ILs soluble in water in the pH range of 3.0-4.0. The extraction efficiency decreases with decrease in the phase volume ratio IL:water. The driving forces governing the phase preference of Quercetin involve hydrophobic interaction, the steric hindrance effect and hydrogen-bonding interaction.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPLEMENTAL MATERIALS

The supplemental materials can be downloaded from the journal website along with the article.

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