Universidade de Aveiro
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Departamento de Química

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From kiwi waste to value-added compounds using biobased solvents

De resíduos de kiwi a compostos de valor acrescentado usando biossolventes

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Bioquímica realizada sob a orientação científica da Doutora Ana Maria da Conceição Ferreira, Investigadora do Departamento de Química, CICECO, da Universidade de Aveiro e coorientação da Doutora Helena Isabel Sousa Passos, Investigadora do Departamento de Química, CICECO, da Universidade de Aveiro.

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Aos meus pais e familiares que me apoiaram neste processo….

o júri

presidente

Prof. Dr. Brian James Goodfellow
Professor Auxiliar do Departamento de Química da Universidade de Aveiro

Prof.ª Dr.ª Maria Olga de Amorim e Sá Ferreira
Professora Adjunta do Departamento de Tecnologia Química e Biológica do Instituto Politécnico de Bragança

Dr.ª Ana Maria da Conceição Ferreira
Investigadora do Departamento de Química da Universidade de Aveiro

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palavras-chave

Extração sólido-líquido, resíduos de kiwi, compostos fenólicos, antioxidantes naturais, biossolventes, processo de otimização.

Resumo

A valorização de recursos naturais ricos em compostos de valor acrescentado é uma das áreas mais relevantes da química sustentável. Os resíduos da indústria do kiwi são uma fonte rica em compostos bioativos, tais como os compostos fenólicos, que exibem atividade biológica com potencial benefício para a saúde. Contudo, os solventes orgânicos voláteis continuam a ser a escolha preferencial para a sua extração. Com o objetivo de desenvolver um processo mais “verde” para a valorização dos resíduos da indústria dos kiwis, este trabalho estuda a utilização de biossolventes (gamma-valerolactona (GVL), cireno e alcanodióis), com caráter hidrotrópico para melhorar a solubilidade e extrair eficazmente os compostos fenólicos das cascas de kiwi *Actinidia deliciosa* 'Hayward'.

Começou-se por avaliar a solubilidade de três compostos fenólicos (catequina, ácido siríngico e ácido ferúlico) em soluções aquosas de biossolventes. Os resultados mostraram o potencial dos biossolventes como hidrótropos, sendo que as soluções aquosas de GVL permitiram incrementos na solubilidade, em comparação com água pura, de até 61, 99 e 237 vezes para catequina, ácido siríngico e ácido ferúlico, respetivamente. Constatou-se também que o mecanismo da hidrotropia depende tanto do hidrótropo como do soluto. O efeito hidrotrópico tende a ser maior para hidrótropos mais hidrofóbicos; no entanto, o aumento da hidrofobicidade dos biossolventes nem sempre é benéfico, pelo que é necessário um equilíbrio entre estes dois efeitos. Por fim, ensaios para aumentar a solubilidade do melhor par hidrótropo-soluto (GVL-ácido ferúlico) através de alta pressão mostraram que a pressão não tem efeito no aumento da solubilidade, apenas permite uma cinética de solubilização mais rápida.

Posto isto, foi realizada a extração de compostos fenólicos de cascas de kiwi utilizando diferentes misturas de biossolventes com etanol e/ou água, sendo as misturas de GVL as mais eficientes. Depois otimizou-se a composição do solvente de extração, sendo a mistura composta por GVL:etanol numa proporção de 7:3 (m/m) a mais eficiente. Posteriormente, utilizou-se uma metodologia de superfície de resposta (RSM) para otimizar as condições de extração para a extração convencional (CE), a extração assistida por ultrassom (UAE) e a extração assistida por micro-ondas (MAE), sendo que a MAE foi a que permitiu obter um extrato com maiores níveis de fenólicos (extratos ricos em epicatequina, ácido cafeico e quercetina) e de atividade antioxidante, num tempo de extração curto. No entanto, o estudo económico mostrou que a UAE é a opção mais viável das técnicas em estudo.

Em resumo, os resultados obtidos demonstraram que os biossolventes combinados com técnicas alternativas podem extrair eficazmente compostos fenólicos das cascas de kiwi, permitindo o desenvolvimento de processos de extração mais sustentáveis, económicos e eficientes na recuperação de produtos naturais de resíduos da indústria alimentar.

Keywords

Solid-liquid extraction, kiwi waste, phenolic compounds, natural antioxidants, biobased solvents, optimization process.

Abstract

The valorization of resources composed of high value-added compounds is one of the most relevant areas of sustainable chemistry. The waste from the kiwi industry is a potential source of bioactive compounds, such as phenolic compounds, which exhibit biological activity with potential health benefits. However, the application of volatile organic solvents for their extraction is still the preferred choice. Aiming to develop a green approach for the valorization of kiwi industry wastes, this work studied the use of biobased solvents (gamma-valerolactone (GVL), cyrene and alkanediols), with hydrotropic character, to improve the solubility, and effectively extract phenolic compounds from *Actinidia deliciosa* 'Hayward' kiwi peels.

First, the solubility of three phenolic compounds (catechin, syringic acid and ferulic acid) in aqueous solutions of biobased solvents were evaluated. The obtained results demonstrated the potential of biobased solvents as hydrotropes for phenolic compounds, with the aqueous solutions of GVL leading to higher increments on the solubility of the phenolic compounds when compared to pure water: up to 61-fold, 99-fold, 237-fold for catechin, syringic and ferulic acid, respectively. It was also demonstrated that the hydrotropy mechanism depends on both hydrotrope and solute. The hydrotropic effect tends to be higher for more hydrophobic hydrotropes, in diluted regions; however, the increase of the hydrophobicity of biobased solvents is not always beneficial, and therefore a balance between these two effects is required. Additionally, experiments to increase the solubility of the best hydrotrope-solute pair (GVL-ferulic acid) through high pressure have shown that pressure has no effect on increasing solubility, it only allows a faster solubilization kinetics.

Afterwards, the effective extraction of phenolic compounds from kiwi peels, using different mixtures of biobased solvents with ethanol and/or water was carried out, with the mixtures of GVL being the most efficient. Then, the best biobased solvent composition was optimized, being the mixture composed of GVL:ethanol in a ratio of 7:3 (wt/wt) identified with the best performance. After, a response surface methodology (RSM) was used to optimize the extraction conditions of conventional extraction (CE), ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE), with MAE being identified as the most promising technique to obtain an extract with high levels of phenolics (mainly composed of epicatechin, caffeic acid and quercetin) and antioxidant activity, in a shorter extraction time. However, an economic study demonstrated that UAE is the preferable extraction technique.

In summary, the results obtained demonstrate that biobased solvents combined with alternative techniques can effectively extract phenolic compounds from kiwi peels, working as a base for the development of more sustainable, economic, and efficient extraction processes to recover natural products from food industry wastes.

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$AA\%$	antioxidant activity (%)
Abs	absorbance (dimensionless);
Abs_{blank}	absorbance of the blank (dimensionless);
$Abs_{control}$	absorbance of the control (dimensionless);
Abs_{sample}	absorbance of the sample (dimensionless);
$\beta 0$	regression coefficient
Bi	linear coefficient
βii	quadratic coefficient
βiii	interaction coefficient
C_H	molar concentration of the hydrotrope (mol/kg)
K_S	Setschenow constant (kg/mol)
K	number of variables that influence the response
K_a	acid dissociation constant (mol/L)
K_{ow}	octanol-water partition coefficient (dimensionless)
R^2	correlation coefficient (dimensionless)
R^2_{adj}	coefficient of determination adjusted (dimensionless)
S	solubility (g/L) or (mol/L)
S_0	solubility in pure water (g/L) or (mol/L)
S/S_0	solubility enhancement (dimensionless)
Xi,j	independent variables
y	response
γ	gamma
λ_{ex}	excitation wavelengths
λ_{em}	emission wavelengths
wt %	weight percentage (%);
wt	weight
x_H	mole fraction of hydrotrope
W	watt

List of abbreviations

AAPH	2,2'-azo-bis(2-amidinopropane)dihydrochloride
ABTS	2, 2’-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)
Ace	acetone
Amp	amplitude (%)
CAE	chlorogenic acid equivalent
CE	conventional extraction
CMC	critical micelle concentration
CtE	catechin equivalent
CUPRAC	cupric reducing antioxidant capacity
CYR	cyrene
DMF	N,N-dimethylformamide
DPPH	2, 2-diphenyl-1-picrylhydrazyl
DW	dry weight
ETG	1,2-ethanediol
EtOH	ethanol
FAO	food and agriculture organization
$FeCl_3$	ferric chloride
FRAP	ferric reducing antioxidant potential
FW	fresh weight
GAE	gallic acid equivalent
GRAS	generally recognized as safe
GVL	gamma-valerolactone
HAT	hydrogen atom transfer
HCl	hydrochloric acid
HEX	1,6-hexanediol
LA	levulinic acid
LGO	levoglucosenone
MAE	microwave-assisted extraction
MeOH	methanol
MHC	minimum hydrotrope concentration
NMP	N-methyl-2-pyrrolidone
ORAC	oxygen radical absorbance capacity
PBS	phosphate-buffered saline

PRO	1,2-propanediol
QE	quercetin equivalent
RE	rutin equivalent
RSLDE	rapid solid-liquid extraction dynamic
RSM	response surface methodology
SBS	sodium benzene sulfonate
SDG	sustainable development goals
SET	single electron transfer
SLE	solid-liquid extraction
STS	sodium toluene sulfonate
SXS	sodium xylene sulfonate
SWE	supercritical water extraction
TFC	total flavonoid content
TPC	total phenolic content
TPTZ	2,4,6-Tris(2-pyridyl)-s-triazine
TE	trolox equivelent
UAE	ultrasound-assisted extraction
USDA	united states department of agriculture

1. Introduction

1.1. Food waste and its possible potential in world industry

Food waste refers to the amount “of food lost or wasted in the part of food chains leading to edible products going to human consumption" [1], being one of the biggest threats to the sustainability of the food system. The food supply chain includes production, handling, storage, processing, distribution and consumption, and at any of these stages, food waste can occur [1]. According to the Food and Agriculture Organization (FAO), about a third of the total global food production and more than 1.3 billion tons of food are wasted [2,3]. Furthermore, it is estimated that around 14% of the world's food is lost from post-harvest to the retail level, as shown in Figure 1 [4]. All these wastes imply that a significant amount of the resources used, and the greenhouse gas emissions caused by them, are not appropriately used to obtain the maximum valorization of produced food. By raising awareness among food industries, retailers, and consumers, mainly in industrialized countries, food waste can be highly reduced [1].

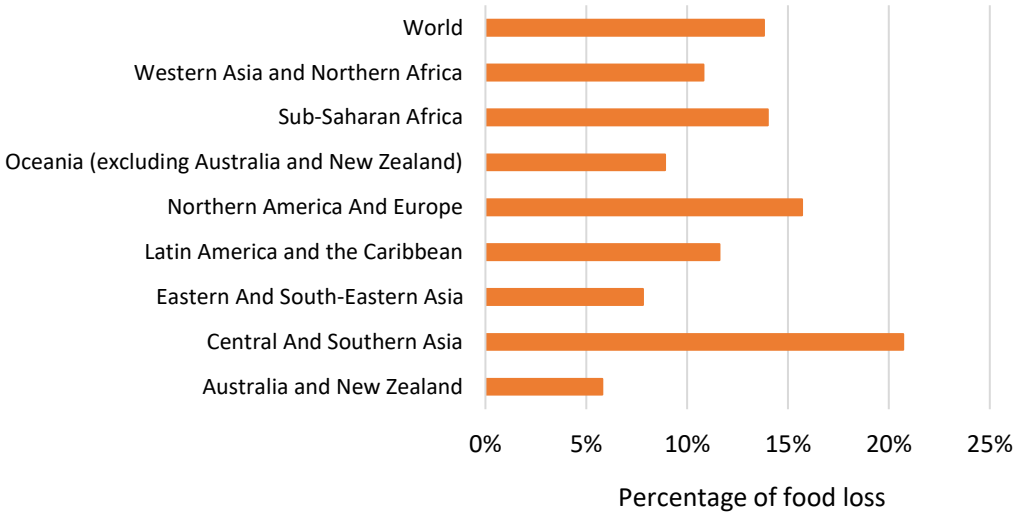

Figure 1. Representation of global percentage of food loss, adapted from [5].

Nevertheless, these wastes can be an important source of bioactive compounds with high-added value, considering that in their composition, high levels of phenolic compounds, vitamins, polysaccharides, dietary fiber, among others, can be found [6]. Most of these compounds have antioxidant, anti-inflammatory, antimicrobial and anticancer properties associated with great beneficial effects in human health [7]. Thus, these by-products from the food industry can be used again to develop natural additives or new foods and/or even functional ingredients to acquire many types of products, namely fertilizers, cosmetic products,

animal feed, among others [6]. The extraction of these high-value compounds from food waste results in the valorization of by-products in line with biorefinery and circular economy concepts, since it allows the waste minimization, efficiency, and valorization of the resources, and consequently decrease of both economic and environmental problems associated to it. Thus, it is crucial to develop sustainable strategies to produce high-quality feedstocks from food waste that is discarded, and improve waste management practices, being this one of the main goals of 2030 Agenda for Sustainable Development Goals (SDG) [8].

It should be highlighted that the food category has been one of the most wasted worldwide, representing around 44% of the municipal solid waste generated in 2016 [8]. Moreover, when analyzing data presented in Figure 2, the category of roots, tubers and oil-bearing crops followed by fruits and vegetables are the most abundant type of food waste, representing 25.3 % and 21.6 %, respectively [4]. The category of fruits and vegetables is a special group, since they are rich in a varied range of bioactive compounds [9], thus the valorization of these residues is extremely important.

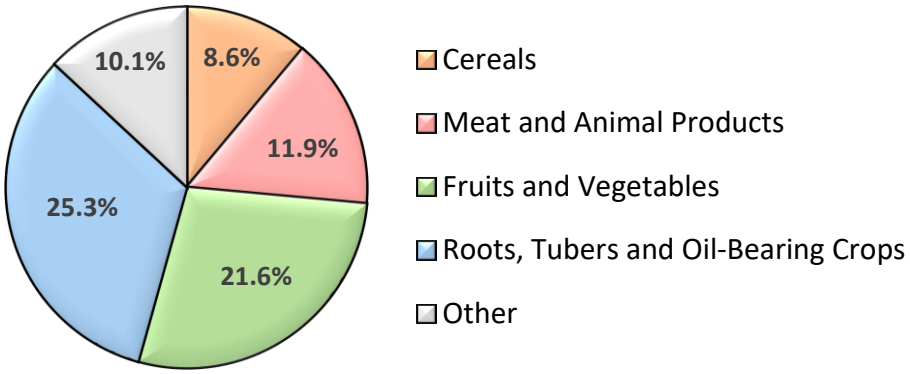

Figure 2. Graphic representation of the percentage of food lost in different food categories, adapted from [5].

1.2. Kiwi: General features, production, and commercialization

Kiwi is a berry that presents numerous locules filled with small black seeds. It is of the genus *Actinidia,* belongs to the *Actinidiaceae* family, which is native from China. This fruit was replanted in New Zealand in the 19th century and gained international commercial importance for the region [10,11]. There are 76 species of kiwi and about 125 known taxa worldwide that have been developed through decades of domestication from the wild kiwi [10,12]. These species present different sizes, shapes, and colors of both peel and flesh (Figure 3) [13]. Among these, the *Actinidia chinensis* (golden-fleshed) and *Actinidia deliciosa* (green-fleshed) species are

the most commercialized due to their admirable flavor and commercial value [14]. *Actinidia deliciosa* presents a bright green flesh with a fuzzy brown peel. This fruit has a larger size, productivity, and lower respiration rate, which determines a longer storage life. On the other hand, *Actinidia chinensis* presents a bright green to a clear intense yellow flesh, bronze, and smooth peel, with a beak shape. This fruit is less hairy than *Actinidia deliciosa* and has short storage life, which can be a problem for its commercialization [12].

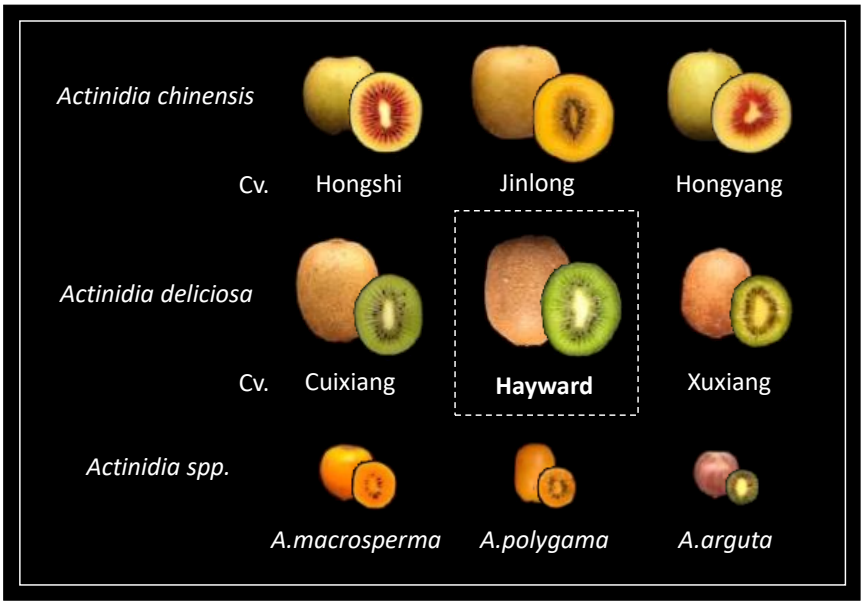

Figure 3. Most commercialized species and cultivars (cv.) of kiwi (*Actinidia deliciosa* and *Actinidia chinensis*) and other minors. Adapted from [7].

The variety *Actinidia deliciosa* 'Hayward' is the most widely grown cultivar in the world, representing around half of all kiwi cultivation [15]. Currently, the world's largest producers are China, followed by New Zealand, Italy and Iran, and they account for about 80% of international kiwi exports [12,16]. Other three countries that contribute on a smaller scale to world exports of fresh kiwi have been the United States, Spain and Portugal [17].

In Portugal, kiwi production started in 1980, and the *Actinidia deliciosa* 'Hayward' has been the main cultivar planted followed by *Actinidia chinensis* cultivars [18]. Another new specie has been introduced in recent years, the *Actinidia arguta* [18]. The expansion of kiwi production to new areas results from an influx of new younger farmers and the development of many different cultivars and the changes in consumer preferences [17,18]. In 2019, Portugal was the 10th kiwi producer in the world with a production volume of 32,000 tons [16]. The main Portuguese producers are in the “Entre-Douro e Minho” and “Beira Litoral” regions, contributing to 83% and

17%, respectively, for the national production. The production area is concentrated in the northwest of Portugal since the climatic conditions of this region are the best for its growth.

In general, 5% to 20% of fruits commercialized are rejected by the market because they do not reach the size or the required appearance [19]. In Portugal, about 30% of the total production of kiwi from 'Hayward' cannot be commercialized because of these requirements, which causes high losses for the producers of kiwis [20]. Usually, the rejected fruits in consequence of their damage are processed in juices, fortified drinks, or winemaking, as well as in jam or canned food after their ripening. However, in kiwi, specifically the 'Hayward' variety (green kiwi), this is not viable due to chlorophyll degradation during processing, which is responsible for the change of the attractive green color present naturally on kiwi. Besides, the characteristic flavor of green kiwi gets lost during processing [12,21]. *Actinidia chinensis* (golden kiwi) presents good results during processing and can be an alternative to food processing, since their natural color (yellow color) resists well in processed products like jam or juices. Nonetheless, this variety presents high prices, so processing these products cannot be possible or viable.

1.2.1. Kiwi nutritional composition

Like all other biological tissues, the composition of kiwi varies accordingly to multiple factors, such as soil type, growing region, horticultural practices, storage and ripening conditions, and, possibly most significantly, the maturity of the fruit [22]. Nutritional composition of *Actinidia deliciosa* 'Hayward' (green kiwi), is described in Table 1 [23].

Table 1. Nutritional composition of *Actinidia deliciosa* 'Hayward' based in the USDA National Nutrient Database for Standard Reference [23].

Nutrient	Units/100 g	*Actinidia deliciosa* (green, raw) Value per 100 g edible flesh
Proximates		
Water	g	83.9
Energy	kcal	58
Energy	kJ	241
Protein	g	1.06
Total lipid (fat)	g	0.44
Ash	g	0.63
Carbohydrate, by difference	g	14
Fiber, total dietary	g	3
Sugars, total	g	8.99
Minerals		
Calcium, Ca	mg	35
Phosphorus, P	mg	34
Potassium, K	mg	198
Vitamins		
Vitamin C, total ascorbic acid	mg	74.7
Vitamin A	µg	4
Vitamin E	mg	1.3

From Table 1 is possible to see that kiwi is rich in fiber, minerals, and vitamins (C, E and A) [24]. Among these, phenolic compounds, and vitamin C (ascorbic acid) are considered the main bioactive components of this fruit. Kiwi has a higher antioxidant capacity and a higher content of phenolic compounds than apple, banana, pear, orange, pineapple, red grapefruit, among others [25]. Thus, this fruit is arousing great interest mainly because it is highly nutritious, has a low caloric value and shows to have the potential to bring high health benefits [22,26].

1.3. Phenolic compounds

Phenolic compounds comprise one of the most significant and fascinating families of substances classified as secondary metabolites in plants, with an extensive range of structures and functions [27]. These secondary plant metabolites are compounds that are not essential to the survival of the whole plant or parts of the plant, however, are no less important [28]. Since one of their functions is to protect the plant, such as in defense responses against herbivores and pathogens and in protection against ultraviolet light, in addition, they perform an important role in the growth and reproduction of plants and act as signal compounds, attracting pollinators or animals for seed dispersion [29,30]. Currently, there is a growing interest in these substances

mainly because of their antioxidant potential and the possible relation between their consumption and the prevention of diseases.

Phenolic compounds are the largest class of food phytochemicals. As a common characteristic, they have an aromatic ring bearing at least one or more hydroxyl groups and range from single aromatic structures, simple molecules (for example, phenolic acids), biphenols (for example, ellagic acid) and flavonoids, which contain two to three aromatic rings to polyphenols containing twelve to sixteen rings [31], as shown in Figure 4. The main classes of phenolic compounds, accordingly, to the human diet, are phenolic acids, flavonoids, and tannins [30]. Flavonoids are the most abundant phenolic compounds in fruits and vegetables (nearly 2/3 of dietary phenolic compounds), and they are the most bioactive. Flavonoids are divided mainly into six subclasses, such as flavones, flavanones, isoflavones, flavonols, flavanols or flavan-3-ols, and anthocyanins [32]. A phenyl benzopyran skeleton forms them: two phenyl rings joined through a heterocyclic pyran ring [31]. Flavonoids differ from each other by the connection position of B and C rings and the saturation, hydroxylation, and oxidation degree of the C ring (Figure 4) [33]. Phenolic acids are the most important group of nonflavonoids in fruits and vegetables. They are composed with a single phenyl group, a carboxylic group and one or more hydroxyl and/or methoxyl groups. Phenolic acids can be divided into hydroxybenzoic acids, hydroxycinnamic acids (Figure 4), and others, differing in terms of length of the chain containing the carboxylic group [31]. Finally, tannins are the third class of phenolic compounds present in fruits and vegetables and are mostly present as phenolic polymers. Tannins exhibit high molecular weight and are water-soluble compounds divided into hydrolysable and condensed tannins [27,34].

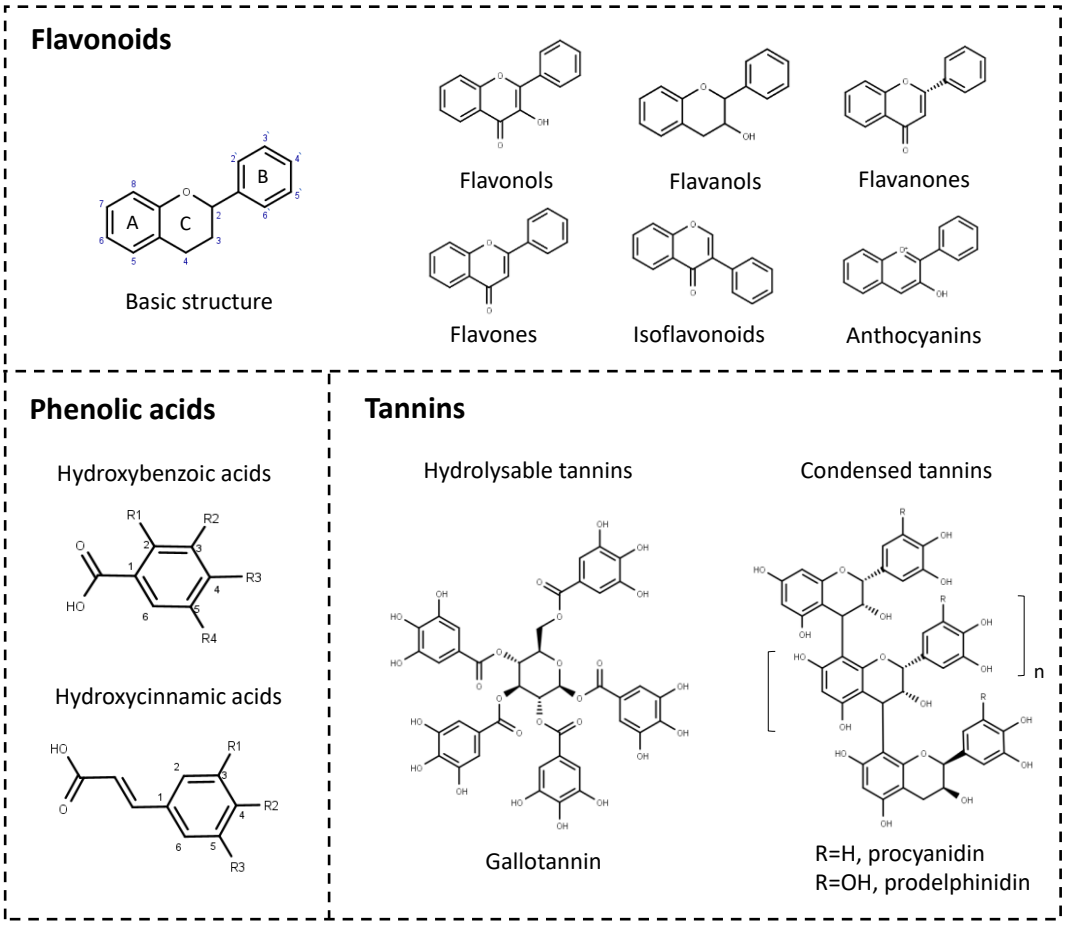

Figure 4. The main classes of phenolic compounds present in fruits and vegetables. Adapted from [31].

1.3.1. Phenolic compounds in kiwi

Phenolic compounds are bioactive compounds widely found in fruits, specifically in kiwi, being mostly represented by flavonoids and phenolic acids [27]. Table 2 summarizes the main constituents of the most commercialized kiwi in the world (*Actinidia deliciosa* 'Hayward'), taking into account different places of production and the different parts of kiwi.

Table 2. Number of phenolic compounds analyzed in different parts of *Actinidia deliciosa* 'Hayward' and in different places of production in the world.

	Production city	Black Sea coast, Turkey [35]	Sichuan and Shaanxi Province, China [7]	Giza, Egypt [36]	Zhouzhi, Shaanxi Province, China [37]	Oliveira do Bairro, Portugal [26]	Yangling, Shaanxi Province, China [38]			Heanam County, Jeonnam Province, Korea [39]	Mei County, Shaanxi Province, China [40]
	Phenolic compounds	fruit (mg/g Exctract DW)	fruit (mg/g Biomass DW)	peel (mg/g Biomass DW)	peel (mg/g Biomass DW)	peel (mg/g Extract DW)	peel (mg/g Extract DW)	seed (mg/g Extract DW)	flesh (mg/g Extract DW)	flesh (mg/g Biomass DW)	flesh (mg/g Biomass FW)
Flavonoids											
Flavanols	Catechin	nd	nd	0.266	0.101	nd	nd	45.340	61.160	nd	0.006
	Epicatechin	nd	nd	nd	nd	163.00	445.620	nd	67.580	nd	0.018
	Procyanidin B1	nd	0.091	nd	nd	nd	nd	nd	nd	nd	0.011
	Procyanidin B2	nd	0.046	nd	nd	nd	nd	nd	nd	nd	0.007
	Procyanidin B3	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.013
Flavonols	Quercitrin (Quercitin-3-*O*-rhamnoside)	nd	0.009	nd	0.001	0.74	nd	nd	nd	nd	nd
	Rutin (Quercetin-3-*O*-rutinoside)	nd	nd	nd	0.002	nd	24.330	22.100	nd	nd	nd
	Quercetin	0.003	nd	0.845	0.006	nd	54.040	nd	33.160	nd	nd
	Kaempferol	nd	nd	nd	nd	nd	53.850	40.090	27.800	nd	nd
	Chrysin acid	nd	nd	1.204	nd	nd	nd	nd	nd	nd	nd
Chalcones	Phlorizin	nd	nd	nd	nd	nd	52.190	24.110	nd	nd	nd
Phenolic acids											
Hydroxybenzoic acids	p-Hydroxybenzoic acid	0.001	nd	nd	0.001	nd	nd	nd	16.500	0.001	nd
	Ellagic acid	0.001	nd	0.172	nd	nd	nd	nd	nd	nd	nd
	Protocatechuic acid	nd	nd	nd	nd	nd	65.950	24.850	23.800	0.014	0.726
	Vanillic acid	nd	nd	nd	nd	nd	nd	14.530	nd	0.005	nd
	Syringic acid	0.001	nd	1.977	nd	nd	65.990	8.450	9.270	0.001	0.084
	Gallic acid	0.003	0.010	0.256	0.009	nd	8.480	nd	6.800	nd	0.008
Hydroxycinnamic acids	Caffeic acid	0.001	nd	0.015	nd	nd	97.310	49.100	nd	0.022	0.002
	p-Coumaric acid	0.004	nd	nd	nd	nd	142.690	53.380	0.710	0.004	0.028
	Ferulic acid	0.002	nd	0.097	0.004	nd	37.290	6.360	0.530	0.002	0.006
	Chlorogenic acid	nd	0.061	nd	0.005	nd	108.320	23.250	1.890	nd	0.004
	Quinic acid	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.010
	Anisic acid	nd	nd	nd	nd	nd	nd	nd	nd	0.001	nd
Phenolic aldehyde	Vanillin	0.002	nd	nd	nd	nd	nd	17.370	nd	nd	nd

DW (dry weight); nd (not detected).

The phenolic composition of each part of kiwi differs significantly as can be observed in Table 2. The peel of kiwi 'Hayward' usually presents a higher phenolic content followed by the pulp and, subsequently, the seeds [26,38,41]. Moreover, Wang *et al.* [38] reported that phenolic compounds, including rutin (22.1 - 24.3 mg GAE/g Extract DW), caffeic acid (49.1 - 97.3 mg GAE/g Extract DW), protocatechuic acid (23.8 - 66.0 mg GAE/g Extract DW), chlorogenic acid (1.9 - 108.3 mg GAE/g Extract DW), quercetin (33.2 - 54.0 mg GAE/g Extract DW), and p-hydroxybenzoic acid (16.5 mg GAE/g Extract DW), were the most abundant in all parts of kiwi, with the highest values found in the peel [38]. Some studies evidenced that the flavanols epicatechin and catechin were the most common polyphenols presented on the peel of kiwi but also, other compounds in minor quantities can be founded, including hydroxycinnamic acids (caffeic acid, p-coumaric acid, ferulic acid and chlorogenic acid) and hydroxybenzoic acids (syringic acid) [26,36,37]. Moreover, a number of investigations referred that the predominant phenolics found in the flesh of green kiwi 'Hayward' were hydroxycinnamic acids, flavonols and the flavan-3-ol epicatechin [7,26,38–40,42]. In relation to kiwi seeds, they also contribute to some fraction of phenolic content in kiwi. In the study of Wang *et al.* [38], the compounds found at higher amount in 'Hayward' seeds were p-coumaric acid, caffeic acid, kaempferol and protocatechuic acid, which is in accordance with others varieties of kiwi assayed in the same study and by other authors [43]. The other varieties, in general present a good concentration on p-hydroxybenzoic acid, quercetin, epicatechin and catechin [38,43]. To sum up, all parts of kiwi are rich in phenolic compounds; still the peel presents the highest concentration on these compounds and is thus the most interesting part to be studied.

1.3.2. Antioxidant activity

Antioxidant activity of phenolic compounds means that these substances can prevent or reduce, at low concentration, the oxidation of a substrate and convert it into an innocuous molecule. Thus, the antioxidant activity determination is important to evaluate food oxidation and deterioration, leading to decreased nutritional value and quality of food [44]. Moreover, the antioxidant activity determination has been one of the topics with great interest to the scientific community looking to better understand the antioxidant potential of food phenolic compounds (specifically flavonoids and phenolic acids), and plant extracts.

There are multiple methods to evaluate antioxidant activity, which are described in the literature. In Table 3 are described the main methods to evaluate antioxidant activity in food and their operating principles. Usually, the methods for determining antioxidant activity in foods are classified into two groups: hydrogen atom transfer (HAT) and single electron transfer (SET)

[45]. HAT occurs when the antioxidant compound extinguishes the radical species by donating hydrogen atoms, and SET occurs when the antioxidant compound transfers a single electron to the free radical. These antioxidant compounds can delocalize around the π-electron system in the aromatic structure to support an unpaired electron [46]. They can also chelate pro-oxidizing metal ions (such as Fe^{2+}/Fe^{3+} and Cu^{2+}), preventing the reaction of free radical propagation in lipid oxidation and maintaining it in redox state, resulting in the formation of nonradical products [47].

Table 3. The main type of assay in food and operating principles. Adapted from [48].

Assay	Radical	Wavelength (nm)	Mode of assay	HAT / ET based	Food matrix
DPPH	DPPH	515	Absorbance	SET based	Lipophilic
ABTS	$ABTS^{+}$	734	Absorbance	SET based	Hydrophilic and lipophilic
FRAP	Chelated Fe^{3+} ions	595	Absorbance	SET based	Lipophilic
ORAC	AAPH (Fluorescein)	λ_{ex}=485 and λ_{em}=538	Fluorescence decay	HAT based	Hydrophilic
CUPRAC	Cu^{2+}, Cu^{+} (complexed with neocuproine)	450	Absorbance	SET based	Hydrophilic and lipophilic

DPPH (2, 2-diphenyl-1-picrylhydrazyl); **ABTS** (2, 2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)); **FRAP** (Ferric reducing antioxidant potential); **ORAC** (Oxygen radical absorbance capacity); **CUPRAC** (Cupric reducing antioxidant capacity); **SET** (single electron transfer); **HAT** (hydrogen atom transfer).

Depending on the nature of compounds present in the food matrix, some methods can be more appropriate than others. For instance, some methods are more adequate to evaluate antioxidant activity in food rich in hydrophilic compounds, while others are better to evaluate antioxidant activity in food rich in lipophilic compounds. However, all of them have in common the presence of an oxidizing agent that reacts with the substrate and, depending on antioxidant activity of the same, the oxidizing agent can be or not neutralized [47].

Currently, and taking into account the strengths, weaknesses and applicability of each test, more than one technique is used to assess the antioxidant capacity, since the use of a single test will not reflect the total antioxidant capacity of a given sample. These methodologies are numerous and each of them is based on different chemical fundaments, being subject to multiple interferences that can be masked using a combination of different methodologies [47].

1.4. Extraction of phenolic compounds

The extraction process is a crucial stage in the isolation and identification of phenolic compounds. To make this process effective and sustainable, it will depend mainly on the choice

of solvent and the extraction method. Depending on the desired compounds and the extraction conditions, many different processes can be used, so there is no single and standard extraction method [49]. The choice on these techniques depends mainly on the scaling processing (laboratory or industrial), the type of biomolecules and matrix, and the ratio between production costs and economic values of the compounds to be extracted [50].

Soxhlet is one of the most traditional solid-liquid extraction techniques that has been used for many decades. However, soxhlet and other conventional techniques present several disadvantages: the use of large amounts of volatile organic solvents, low extraction selectivity, high time consuming, and the thermal decomposition of thermolabile compounds [51,52]. New extraction methods have been developed to overcome the previous disadvantages namely, supercritical fluid extraction [53], ultrasound-assisted extraction [54], microwave-assisted extraction [55], accelerated solvent extraction [54], among others. These techniques showed to be more efficient and fast for the extraction of compounds from plant matrices, since most of them can work at elevated pressures and/or temperatures [52]. However, for thermolabile compounds, extraction at high temperatures can cause solute degradation, thus the extractions conditions must be strictly controlled to avoid this possibility [56]. These new procedures reveal a great potential to extract high-value components, which can be used in different industries, as nutritionally and pharmacologically functional ingredients [50].

Solid-liquid extraction techniques with conventional organic solvents are the most commonly used techniques for extracting and isolating phenolic compounds [49]. Regarding the solid-liquid extraction, this technique allows extracting compounds from solids (biomass), generally using organic solvents, mixed or pure, based on two fundamental principles: diffusion and/or osmosis [57]. Specifically, this technique involves the following steps: contact, penetration, and diffusion of the solvent in the solid matrix which contains the solute of interest and solubilization and transfer of the solute from the solid medium to the liquid medium, as can be seen in Figure 5.

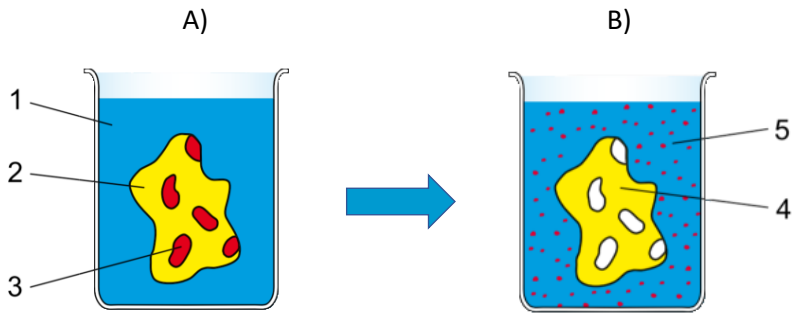

Figure 5. Process of solid-liquid extraction. Before extraction (A) and after extraction (B): **1-** solvent; **2-** solid matrix; **3-** solute of interest; **4-** extraction of the solute of interest; **5-** solute of interest in the solvent. Adapted from [58].

The solvent to be used must be carefully selected to avoid matrix interferences, and experimental parameters such as, solid-liquid ratio, solvent polarity, particle size, stirring rate, extraction time, pH and temperature, must be optimized to efficiently extract the target compounds [59]. However, this technique presents some drawbacks related to the use of volatile organic solvents since some of them are explosive, inflammable, and toxic [50]. Currently, the use of volatile organic solvents tends to be reduced and replaced by green solvents of low price and combined with other extraction techniques. These green/alternative solvents would be, for instance, water and aqueous solutions of non-toxic and sustainable solvents and also Generally Recognized As Safe (GRAS) solvents [50,60].

1.4.1. Extraction of phenolic compounds from kiwi

Solid-liquid extraction is the most used technique for extracting phenolic compounds from kiwi, mainly due to its broad applicability and simplicity [61]. However, new investigations employed other techniques that improved the safety and efficiency of the traditional ones, including subcritical water extraction (SWE) and microwave-assisted extraction (MAE). For instance, Carbone *et al.* [62] optimized the extraction of bioactive compounds from kiwi pomace through MAE using ethanol:water (1:1) at 75 °C for 15.0 min. The optimized extract showed higher total phenolic content (TPC: 4.8 mg GAE/g DW) than conventional techniques reported in the literature for kiwi pomace (TPC: < 2.0 mg GAE/g DW) [62]. Kheirkhah *et al.* [61] evaluate the effect of applying SWE, *i.e.* water in subcritical state (200 °C at 50 bar), in the extraction of phenolic content from kiwi pomace. The results showed that SWE leads to better extraction results (TPC: 60.5 mg CtE/g DW) than conventional SLE using acetone:water (7:3) at 25 °C (TPC: 8.1 mg CtE/g DW) [61]. Thus, it seems that high temperature and pressure allow to enhance water properties in order to improve the extraction of the polar compounds (phenolic

compounds). Additionally, Guthrie *et al.* [63] also verified that SWE using subcritical water (160 °C, at 30 bar and water with pH 2) allows a more efficient extraction of phenolic antioxidants (TPC: 51.2 mg GAE/g DW) from kiwi peels than when used the conventional SLE with a mixture of ethanol:water (1:1), at pH 2 (TPC: 26.2 mg GAE/g DW). All these studies support the high efficiency of greener extraction techniques for the valorization of the kiwi and the recovery of phenolic compounds. However, the use of these new solid-liquid extraction techniques is still an unexplored topic in kiwi literature that needs to be better studied and developed in the future.

The extraction of phenolic compounds in kiwi and other fruits has been done using organic solvents, namely ethanol, methanol, and acetone (Table 4). According to Deng *et al.* [43] the extraction of phenolic compounds depends essentially on the polarity of solvents and compounds, thus the use of a single solvent may not be so effective for isolation of a bioactive compound as the combination of solvents. It was demonstrated that polyphenol solubility in pure solvent drops remarkably, while in the presence of water, the extraction efficiency increases [43]. Therefore, extractions with organic solvents, in these studies, are usually done together with water, as shown in Table 4. On the other hand, Ma *et al.* [64] and Du *et al.* [65] used a mixture of two organic solvents, ethanol:acetone (7:3 v/v), to extract phenolic compounds from kiwi´s pulp and flesh, respectively. The results showed an extraction with low levels in phenolic content (TPC: 0.42 mg GAE/g FW), particularly in the flesh, compared to the other studies that used organic solvents combined with water (majority, TPC > 1 mg GAE/g FW) (Table 4) [38,66]. Mixtures of ethanol in water was one of the solutions that showed to be adequate to extract phenolic compounds with great antioxidant activity and other activities [26,38,67–70]. Additionally, ethanol is regarded as less toxic and of lower risk to human health than the other organic solvents, so its use in the extraction process is advantageous [71]. Hence, it is important to use a mixture of solvents, specifically in combination with water, to efficiently extract phenolic compounds. Aqueous solutions of ethanol are considered, in general, as the best and safe to extract a higher number of phenolics as also with great antioxidant activity.

Table 4. Summary of solvents, extraction conditions, total phenolic content (TPC) and total flavonoid content (TFC) in different kiwi 'Hayward' parts.

Part	Solvent	Extraction conditions (type, T, t)	TPC (mg/g)	TFC (mg/g)	Ref.
Peel	water	SLE, 25 °C, 24 h	15.64[a]	13.15[f]	[36]
	methanol-water (8:2, v/v)	SLE, 25 °C, 24 h	15.72[a]	13.12[f]	
	ethanol-water (8:2, v/v)	SLE, 25 °C, 24 h	14.68[a]	11.69[f]	
	acetone-water (8:2, v/v)	SLE, 25 °C, 24 h	24.54[a]	24.47[f]	
	ethanol-water (7:3, v/v)	SLE, < 45 °C, 1h	~22[a]	4.5[h]	[38]
	subcritical water	SWE, 160 °C, 20 min	51.2[a]	22.5[c]	[63]
	ethanol: water (1:1, v/v)	SLE, 25 °C, 24 h	26.15[a]	18.93[c]	
	ethanol-water (9.6:0.4, v/v)	SLE, 25 °C, 1 h	1.54[d]	--	[72]
	methanol	SLE, 25 °C, 20 min	8.20[a]	--	[73]
Pulp	ethanol-water (9.6:0.4, v/v)	SLE, 25 °C, 1 h	1.09[d]	--	[72]
	ethanol-water (8:2, v/v)	SLE, 25 °C, 1 h	0.50[a]	0.46[f]	[74]
	ethanol: acetone (7:3, v/v)	SLE, 37 °C, 1 h	~1.02[b]	~1.20[d]	[75]
	water	SLE, 25 °C, -	1.40[b]	--	[76]
Flesh	methanol: water (8:2, v/v)	SLE, -, -	--	92.1[c]	[39]
	metanol	SLE, -, -	9.60[a]	--	
	ethanol-water (7:3, v/v)	SLE, < 45 °C, 1h	~11[a]	~1[h]	[38]
	acidified methanol (v/v)	SLE, 35 °C, 3 min	0.49[b]	0.41[d]	[40]
	water	SLE, 25 °C, -	5.30[a]	0.57[c]	[69]
	ethanol	SLE, 25 °C, -	4.48[a]	1.22[c]	
	acetone	SLE, 25 °C, -	1.15[a]	0.61[c]	
	hexane	SLE, 25 °C, -	0.49[a]	0.42[c]	
	water	SLE, -, -	0.71[b]	0.04[d]	[77]
	water	SLE, 25 °C, -	5.47[a]	1.65[c]	[68]
	ethanol	SLE, 25 °C, -	5.41[a]	1.09[c]	
	methanol: water (7:3, v/v)	SLE, -, -	1.62[e]	--	[66]
	methanol	SLE, 25 °C, 20 min	5.50[a]	--	[73]
	ethanol:acetone (7:3, v/v)	SLE, 37 °C, 1 h	0.42[b]	0.07[i]	[65]
Fruit	water	SLE, 25 °C, 24 h	16.67[a]	12.95[f]	[35]
	acidified methanol-water (7:3, v/v)	SLE, 25 °C, 60 min	3.75[a]	--	[7]
Seed	ethanol-water (7:3, v/v)	SLE, < 45 °C, 1h	~6[a]	~2.5[h]	[38]
Leaves	water	SLE, 100 °C, 10 min	~25[a]	--	[78]
Pomace	ethanol: water (1:1, v/v)	MAE, 75 °C, 15 min	4.79[a]	--	[62]
	subcritical water	SWE, 200 °C, 90 min	60.53[c]	24.62[f]	[61]
	ethanol: water (8:2, v/v)	SLE, 25 °C, 2 h	~6[c]	~2[f]	
	methanol: water (8:2, v/v)	SLE, 25 °C, 2 h	~4[c]	~2[f]	
	acetone: water (8:2, v/v)	SLE, 25 °C, 2 h	8.1[c]	~4[f]	

[a]mg GAE/g of dry weight (DW); [b]mg GAE/g of fresh weight (FW); [c]mg CtE/g of dry weight (DW); [d]mg CtE/g of fresh weight (FW); [e]mg CAE/g of fresh weight (FW); [f]mg QE/g of dry weight (DW); [g]mg QE/g of fresh weight (FW); [h]mg RE/g of dry weight (DW); [i]mg RE/g of fresh weight (FW); [j]mg CAE/g of dry weight (DW); SLE, Solid-liquid extraction; SWE, Supercritical water extraction; MAE, Microwave-assisted extraction; GAE, gallic acid equivalent; CtE, catechin equivalent; CAE, chlorogenic acid equivalent; QE, quercetin equivalent; RE, rutin equivalent.

Concerning the use of ethanol as the best solvent for the extraction of phenolic compounds, some topics need to be discussed. According to Leontowicz *et al.* [68] pure water extracts presented a higher content of polyphenols than pure ethanolic extracts at normal pressure, in different kiwi varieties. The water extracts presented slightly higher content of flavonoids and tannins, and lower content in flavanols compared to ethanolic extracts. These results are in accordance with the solubility of each compound in the different solvents and the kiwi variety and parts used for the extraction, which explains the significant differences in the contents of bioactive compounds in the extracts obtained [79]. Moreover, Salama Zeinab *et al.* [36] evaluated four different solvents (water, ethanol, methanol, and acetone) in their capacity to extract phenolic compounds of the peels of kiwi, and the highest content on phenolic compounds was obtained in acetone extract (TPC: 24.54 mg GAE/g DW). Thus, this solvent might be a promising solvent for the extraction of these compounds from kiwi peels. Another study evaluated the extraction efficiency of different solvents (water, ethanol, acetone, and hexane), but in this case was used the flesh of kiwi [69]. According to this investigation, the ethanolic extract was the best, with a higher phenolic content (TPC: 5.30 mg GAE/g DW). Thus, the part of the fruit used to do the extraction will also interfere in the results since each part contains different amounts of compounds, or even different compounds, which will be evidenced in the solubility on a specific solvent. Overall, the compounds present in the extracts have different solubilities in different solvents, and the use of aqueous solutions of organic solvents can embrace a higher number of compounds extracted.

1.5. Conventional solvents *vs.* alternative solvents

Nowadays, the extraction of bioactive compounds from food industry waste is increasingly applied. However, conventional extraction techniques and traditional solvents are changing due to process sustainability issues, aiming to develop an extraction process that maintains our planet health.

According to the principles of green chemistry, which is also known as sustainable chemistry, volatile organic solvents must be reduced or even eliminated in chemical processes, and should be replaced by environmental solvents that have a minimal impact on both environment and human health [80]. Therefore, in recent years, sustainable issues associated with the use of conventional solvents (organic solvents), induced the development and application of alternative and more environmental friendly solvents, such as ionic liquids, eutectic solvents, supercritical fluids (for example, CO_2), water, water-rich solutions (usually of surfactants), fluorous solvents and polymers [81,82]. Despite the promising advantages of these alternative

solvents, most part present some disadvantages, namely high cost and high energy consumption associated to their recovery and purification, and therefore they are not widely used in industry as desired [81,82].

1.5.1. New green solvents

In the same line, new green sustainable solvents derived from renewable sources, known as biobased solvents, have been introduced as less toxic and more biocompatible than the organic volatile compounds [83,84], being thus an environmentally friendly option in the extraction of bioactive compounds from natural sources. Some of them include alkanediols [85] and more recently, the dihydrolevoglucosenone (cyrene) [86] and gamma-valerolactone (GVL) [87]. Cyrene and GVL are becoming more and more studied and popular as alternative renewable green solvents [88,89]. Some of these biobased solvents are approved by the European Commission as food additives [90,91], because they present minimal toxicological concerns, which means they can remain in the extract for a food application without removing them, what is a big advantage in extraction and purification processes, since the expensive step of solvent recovery can be avoided.

GVL is frequently used as a food additive and can be found naturally in fruits [83]. GVL is readily obtained from cellulose, which is derived from lignocellulose biomass (40 to 50 % of cellulose), an abundant and cheap material (Figure 6A). GVL exhibits remarkable characteristics of an ideal sustainable liquid: is non-toxic, non-volatile (6.5 mbar at 258 ^{o}C), water-soluble, zeotropic (when mixed with water), has a high boiling point (207 ^{o}C), a low melting point (-31 ^{o}C) and a recognizable herbal odor, which makes it easy to detect in case of leaks and spills. When GVL is combined with water, produce an azeotropic mixture, making GVL easy to recycle [83,92]. An important property is that GVL is a stable chemical since does not suffer oxidation and degradation under standard temperature and pressure, making it a safe substance for many processing industrial applications, such as storage, and transportation [83,89].

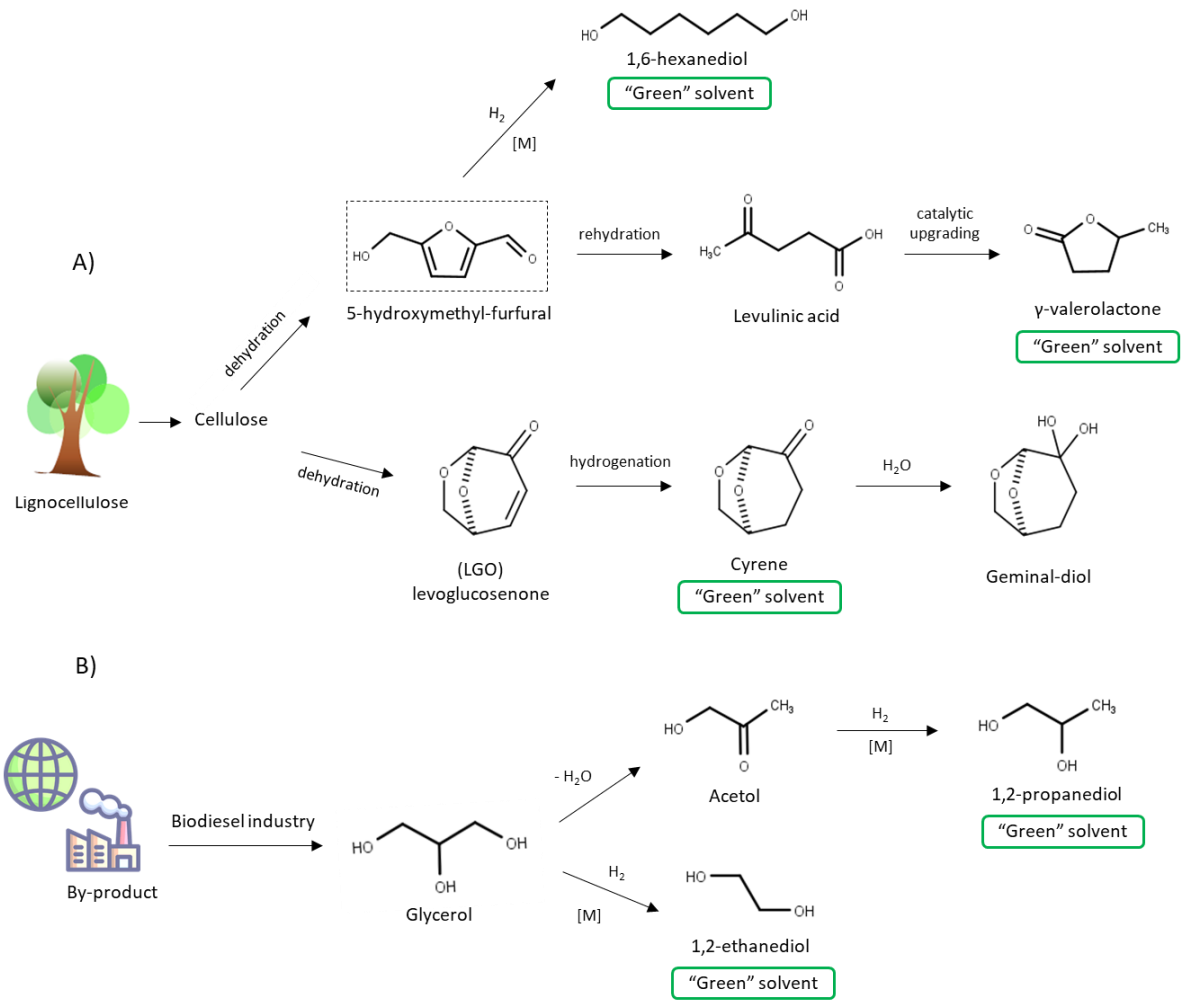

Figure 6. General scheme of biomass processing to "green" solvents, such as GVL, cyrene and alkanediols (1,2-ethanediol, 1,2-propanediol, and 1,6-hexanediol). Renewable solvents derived from A) lignocellulose biomass and from B) glycerol, a by-product from biodiesel industry. Adapted from [93–95].

Cyrene is a dipolar aprotic solvent that could substitute traditional aprotic solvents, like N-methyl-2-pyrrolidone (NMP) and N,N-dimethylformamide (DMF). Similarly, to GVL, cyrene is also obtained from cellulose, but not from levulinic acid, but from levoglucosenone (LGO) (Figure 6A) [96]. In fact, when cyrene interacts with water occurs the formation of cyrene's geminal diol, which hydrogen bonding increases [88]. The cyrene-water mixture is characterized as barely ecotoxic, bioderived, not mutagenic, and with tunable hydrophilic/hydrophobic properties [84,88]. On opposite to GVL, questions about the stability of cyrene under long term processes or harshness can limit its use in some applications.

Alkanediols, a subgroup of diols, have a linear or branched hydrocarbon chains containing exactly two hydroxyl groups in different positions. Renewable alkanediols such as

1,2-ethanediol, 1,2-propanediol, and 1,6-hexanediol, have significant commercial value for their own alternative green solvent properties [97]. All the three solvents have applications in the cosmetic industry, while only 1,2-propanediol is used in the food industry [98–100]. They can be easily obtained from biomass sources by different methods [101]. Both 1,2-ethanediol and 1,2-propanediol are obtained by glycerol hydrogenolysis, the major by-product from the biodiesel industry (Figure 6B) [93]. 1,6-hexanediol is not obtained from glycerol, but from 5-hydroxymethylfurfural (HMF), such as GVL (Figure 6A) [102].

1.5.2. Hydrotropy as a rule in the extraction of biocompounds from biomass

Among all solvents that can be applied for the extraction of bioactive compounds, water (or aqueous mixtures) appears as the greenest option. It is environmentally benign and inexpensive, non-flammable and non-toxic, which are great advantages in terms of pollution prevention and cleaning processes development [83,103]. The use of water as a solvent can provide higher efficiency in the extraction of the target compounds, since it confers a lower viscosity to the solution, allowing to increase the mass transfer and reduce energy consumption [104,105]. Nevertheless, the low solubility of bioactive compounds in water can be a problem because it limits the use of this solvent in an efficient biomass extraction [52]. However, to solve this problem, additives such as hydrotropes and surfactants can be used to increase the solubility of bioactive compounds in aqueous solutions [106].

Hydrotropes are a class of compounds that enhance the solubility of hydrophobic compounds in aqueous solution [107]. They can stabilize aqueous solutions and tailor their viscosity [107,108]. Hydrotropes are amphiphilic substances characterized mainly by hydrophilic functional group (anionic group) attached to another group, typically an hydrophobic aromatic ring (cationic group), in which interaction is limited to dispersion contributions [109]. Despite having an amphiphilic structure, these compounds do not work as surfactants because the hydrophobic fraction is very small. Hydrotropes classes can be anionic, cationic or non-ionic amphiphiles. For example, sodium toluene sulfonate (STS), sodium xylene sulfonate (SXS), sodium benzene sulfonate (SBS), nicotinamide and urea are hydrotropes of ionic organic salts; ethylene glycol ethers and propylene glycol ethers are non-ionic alkyl-hydrotropes [107,110]. Their property of enhancing the solubility of hydrophobic compounds is still not well understood [111]. There are speculations that the mechanism of hydrotropy is related with: (a) pre-clustering of hydrotropes analogous to micellar solubilization [112]; (b) hydrotrope-solute complex with a specific stoichiometry [113]; (c) hydrotrope behaving like chaotropic agents and weakening the hydrophobic effect disrupting “water structure” [114]. Nevertheless, these

hypotheses are not supported by statistical thermodynamics descriptions of hydrotropy. A recent study developed by Abranches *et al.* [111], using statistical thermodynamics description, showed that apolarity of hydrotrope and solute is the driving force of hydrotropy, and the presence of water strengthens the interaction of hydrotrope-solute. More specifically, when the apolarity of the hydrotrope and solute are the same, the number of hydrotropes aggregated around the solute is maximum, increasing the solubility of the solute. On the other hand, when the apolarity of the hydrotrope is smaller or bigger than the solute, the driving force for aggregation hydrotrope-hydrotrope is low or larger than hydrotrope-solute, respectively, decreasing the solubility of the solute. This means that agglomeration of hydrotrope-solute is driven by a strong hydrophobic or water-mediated interaction [111,115]. These results are very important for understanding the water-mediated aggregation of hydrotrope molecules around the solute hypothesis. However, many studies need to be done to deeply understand the mechanism of the hydrotropy.

Finally, recent studies show that these biobased solvents (monoalkylglycerol ethers [111], glycerol ethers [110] and cyrene [116,117]) can act as hydrotropes, increasing the solubility of phenolic compounds in water, which supports the idea that these solvents can be used as alternative solvents in the extraction of phenolic compounds (syringic acid, gallic acid, vanillin). For example, aqueous mixtures composed by 1,2-ethanediol and 1,2-propanediol demonstrated to be efficient in the extraction of phenolic compounds (quercetin, coumaroylquinic acid, caffeoylquinic acid) from walnut leaves [85]. Despite their potential, biobased solvents have been scarcely investigated in the extraction of phenolic compounds from natural sources (biomass), not even been used in the extraction of phenolic compounds from kiwi. Specifically, GVL and cyrene have not yet been used as extraction solvents in any study. Based on this lacuna and in alignment with the valorization of kiwi, these biobased solvents appear as alternative solvents to develop sustainable extraction processes of phenolic compounds from kiwi waste.

1.6. Scopes and Objectives

Kiwi is a fruit widely produced in Portugal. However, almost one-third of the total production is wasted due to commercial pre-requisites [20]. This waste can be reused since kiwi is rich in high value-added compounds, mainly phenolic compounds with potential to be applied in food, pharmaceutical and chemical industries. The main reason for their higher applicability is their broad range of biological activities and related health benefits, such as strong anti-inflammatory, antioxidant, and antimicrobial properties [27]. Although highly relevant, phenolic compounds extraction from biomass is usually carried out with volatile organic solvents [118].

One of the major limitations to the development of a sustainable extraction process for the recovery of phenolic compounds from biomass, is their low solubility in water. To overcome this obstacle, the solubility of phenolic compounds in aqueous solutions can be increased by the use of additives, such as hydrotropes [107]. Recently, it was demonstrated the ability of alternative renewable solvents, such as biobased solvents, to act as hydrotropes, since they improved the solubility of hydrophobic compounds, like phenolic compounds, in water [117]. In this context, the main objective of this work is to study the application of alternative biobased solvents to improve the solubility and effectively extract phenolic compounds from kiwi wastes.

The first step of this work was to determine the solubility of the phenolic compounds (catechin, syringic and ferulic acid) in aqueous solutions of a wide range of biobased solvents (GVL, cyrene, 1,6-hexanediol and 1,2-propanediol), and concentrations, in order to understand the effects of biobased solvents' concentration and structure on the solubility of phenolic compounds at 30 °C in aqueous solutions. Moreover, to deepen the understanding of hydrotropy mechanism, the Steschenow constant was calculated to study the hydrotropic effect at diluted regions and was also applied the cooperative hydrotropy model to describe the interaction phenomenon between solute and hydrotrope in the entire concentration range of the hydrotrope. All these tests allowed a deeper insight into the mechanism of hydrotropy at the molecular level.

The second part of this work addresses a study regarding the combination of biobased solvents, and alternative extraction techniques for the recovery of phenolic compounds from kiwi peels of *Actinidia deliciosa* 'Hayward', with the aim of developing a green approach for the valorization of kiwi waste. It starts with a screening of the most suitable biobased solvents, and their mixtures with ethanol and water, through the comparison of the extracts obtained, regarding their phenolics content (by TPC assay), and antioxidant activity (by ABTS and FRAP assays) levels. After selecting the best solvent, the extraction conditions for each extraction technique were studied and optimized, in order to compare the extraction efficiency of advanced techniques (UAE and MAE), with the conventional extraction (CE). The extraction conditions (temperature/amplitude, extraction time and the solid-liquid ratio) were optimized by the response surface methodology (RSM), in order to obtain an extract rich in phenolic compounds, with a maximum of antioxidants from kiwi peels. Then, the identification of the mainly phenolic compounds of the optimized extracts was carried out by ultra-high pressure liquid chromatography with mass spectrometry with ultraviolet detection (UHPLC-UV-MS^n) for each technique. Moreover, the extraction efficiency of the conventional solvents was compared with the optimized mixture of biobased solvent for each extraction technique in study, at the optimized conditions, in order to verify the advantage of using green chemistry tools on the

valorization of food waste. Finally, an economic study (in a simple way) was carried out to understand which is the most promising extraction technique in the extraction of phenolic compounds from kiwi peels; considering variables such as the energy consumed, the price of the extraction solvent, the optimal extraction conditions and the TPC value achieved for each technique.

2. Material and Experimental Procedure

2.1. Materials

The chemical compounds used in this work are summarized in Table 5 and the respective structures are presented in Figure 7. The water (H_2O) was double distilled, passed across a reverse osmosis system, and further treated with a Milli-Q plus 185 H_2O purification device.

Table 5. List of substances used in this work, including the abbreviation, CAS number, purity (wt %) and source.

Compound	Abbreviation	CAS number	Purity	Source
[2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate)]	ABTS	30931-67-0	98 wt %	Sigma
Acetic acid	---	64-19-7	≥99.7 wt %	Fisher Chemical
Acetone	Ace	67-64-1	100 wt %	Fisher Scientific
Acetonitrile HPLC grade	---	75-05-8	>99 wt %	Sigma
(+)-Catechin hydrate	---	225937-10-0	>98.0 wt %	Sigma
Cyrene	CYR	53716-82-8	99 wt %	Sigma-Aldrich
1,2-Ethanediol	ETG	107-21-1	99.5 wt %	Carlo Erba
Ethanol	EtOH	64-17-5	99.0 wt %	Fisher Scientific
Ferulic acid	---	537-98-4	99 wt %	TCI
Folin-Ciocalteu	---	n.a.	for Clinical diagnosis	Panreac
Formic acid	---	64-18-6	>98.0 wt %	Sigma
Gallic acid	GA	149-91-7	99.5 wt %	Merck
Hydrochloric acid	HCl	7647-01-0	37 wt %	Honeywell
1,6-hexanediol	HEX	629-11-8	97 wt %	Acros Organics
Iron (III) chloride hexahydratate	---	10025-77-1	99 wt %	Merck
Methanol	MeOH	67-56-1	99.8 wt %	Fisher Chemical
1,2-propanediol	PRO	57-55-6	99.5 wt %	Sigma-Aldrich
Potassium persulfate	---	7727-21-1	extra pure	Scharlau

Sodium acetate	---	127-09-3	99 wt %	Prolabo (JMS)
Sodium carbonate	---	497-19-8	99 wt %	Vencilab
Sodium hydroxide	--	1310-73-2	98 wt %	Fisher
Syringic acid	---	530-57-4	>97 wt %	Acros Organics
2,4,6-Tris(2-pyridyl)-s-triazine	TPTZ	3682-35-7	>99 wt %	Sigma-Aldrich
Trolox	---	53188-07-1	97 wt %	Acros Organics
Water HPLC grade	---	7732-18-5	99 wt %	Supelco
Gamma-valerolactone	GVL	108-29-2	98 wt %	Acros Organics

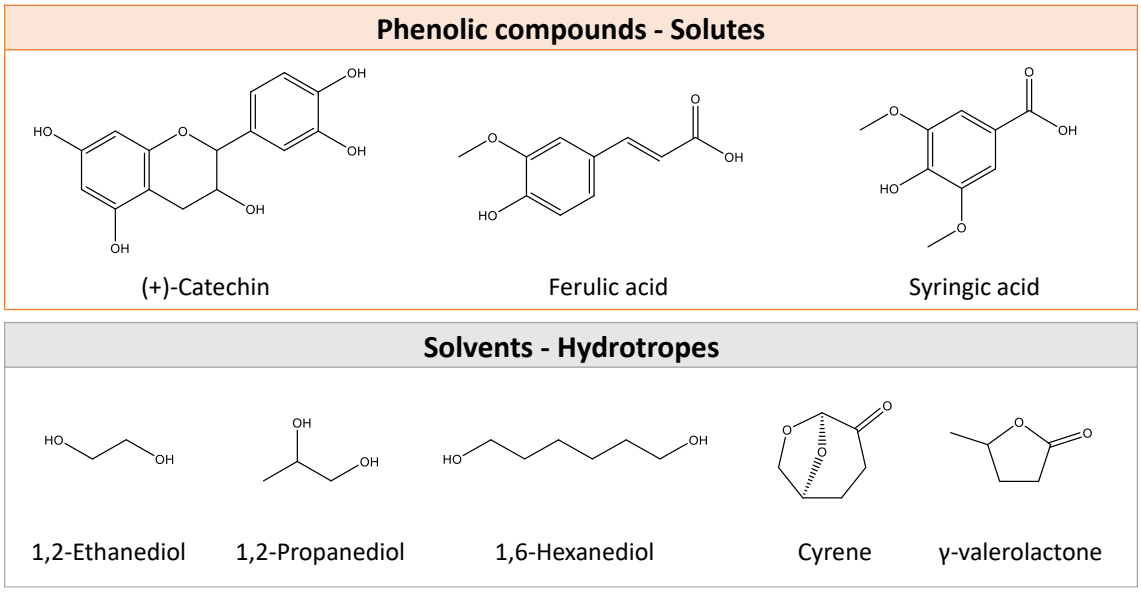

Figure 7. Chemical structure of the phenolic compounds and biobased solvents used in this work.

2.2. Experimental procedure

2.2.1. Solubility measurements

The solubility of the three phenolic compounds (catechin, syringic and ferulic acid) in aqueous solutions of biobased solvents (GVL, CYR, PRO and HEX) were determined using the analytical isothermal shake-flask methodology, previously described in literature [110]. These aqueous solutions of biobased solvents or pure biobased solvents were prepared gravimetrically within ± 10^{-4} g by using an analytical balance Mettler Toledo Excelence – XS205 Dual Range. The solutes, including syringic acid, ferulic acid and catechin, were added in excess to a fixed volume of each aqueous solution of biobased solvents or water. The samples were equilibrated in an air

oven under constant agitation (1150 rpm) at (30 ± 1) °C and for a minimum of 72 h, using an Eppendorf Thermomixer Comfort equipment.

After equilibrium was reached, the mixtures were placed in an oven at 30 °C, for 72 h, in order to separate the macroscopic solid phase from the liquid phase. Then, the liquid phase of each sample was carefully collected and diluted in distilled water. The quantification of ferulic acid, syringic acid and catechin was carried by a UV-spectrophotometry using a SYNERGY|HT microplate reader, BioTek at a wavelength of 316 nm, 266 nm and 278 nm, respectively, using the calibration curves (Figure A.1.1-A.1.3, Appendix A.1) previously established. Blank control samples were made in order to eliminate the interference of aqueous solutions of biobased solvents. For each concentration three individual samples were prepared to determine the average and standard deviation of the results.

2.2.2. Solubility measurements at high pressure

The solubility measurements at high pressure were carried out with water and aqueous solutions of biobased solvents (GVL). These solutions were prepared gravimetrically within ± 10^{-4} g. The solute, ferulic acid, was added in excess to a fixed solvent volume (20 mL) in high pressure cells. These solutions were incubated for 24 h or 48 h, at a constant agitation of 1150 rpm, 30 ^{o}C, and normal pressure (1 bar) or high pressure (100 bar) using a Shaker IKA equipment. On the experiments carried out at 100 bar, the saturated liquid phase was collected under high pressure with a syringe. The collected liquid phase was diluted in distilled water and the quantification of ferulic acid was carried by UV-spectroscopy, at a wavelength of 316 nm, as previously described in the chapter 2.2.1. Blank control samples were prepared to eliminate the interference of aqueous solutions of biobased solvents.

2.2.3. pH measurements

The pH of biobased solvents aqueous solutions (hydrotopes) before and after the saturation was measured using a METTLER TOLEDO SevenMulti pH meter within an uncertainty of ± 0.02. pH buffer solutions at 4.00, 7.00 and 9.00 were used for calibrating pH electrodes.

2.2.4. Biomass collection, selection and storage

Kiwi (*Actinidia deliciosa*) belonging to the 'Hayward' cultivar were purchased at a local producer from Vila Nova de Famalicão, Braga, Portugal. Kiwi were peeled, and then processed into juice and pulp. Whole kiwi (with peel) was also processed in a blender. The obtained samples (peels, pulp, juice and whole kiwi) were stored at -80 °C. Before the extraction, samples

were immersed into liquid nitrogen and grounded in a coffee grinder to obtain a "powder". To select the kiwi part richest in phenolic compounds, soxhlet of each type of sample (peels, pulp, juice, and whole kiwi) was performed for 6 h, using EtOH as the solvent, and a solid-liquid ratio (mass of biomass (g) per volume of solution (mL)) of 0.03. The kiwi peels were selected as the biomass with the highest content of phenolic compounds (see Table A.2.1 and Figure A.2.1, Appendix A.2), being the biomass used in the following studies. Before starting the screening of biobased solvents for the extraction of phenolic compounds, the impact of the storage procedure on the phenolic content of selected biomass peels was evaluated. In this study was used biomass stored under three different conditions: (i) dried at room temperature and then stored at -10 °C; (ii) stored at -10 °C and (iii) stored at -80 °C. After a minimum of two weeks, the samples stored at different conditions were analyzed, with storage at -80 °C being the one selected to maintain the biomass during the development of this work (see Table A.2.2 and Figure A.2.2, Appendix A.2). The choice of the biomass and its storage conditions was made based on the total phenolic content (TPC), and antioxidant activity of the extracts, by the ferric reductive antioxidant power (FRAP) and [2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate)] (ABTS) methods (described below).

2.2.5. Screening of biobased solvents for the extraction of phenolic compounds

A screening was performed using the following biobased solvents: ETG, PRO, HEX, CYR and GVL. Each of these solvents were applied as binary mixtures by combining them with H_2O or EtOH in the weight ratios 3:7 and 7:3. The proportions chosen were based in the results obtained in literature [38] and in the solubility tests. These were also used in ternary mixtures composed of biobased solvent, EtOH and H_2O in the weight ratio of 4:4:2 respectively. All mixtures were prepared gravimetrically with an uncertainty of ± 10^{-4} g. The extraction of phenolic compounds from kiwi peels were carried out in a Carousel Radleys Tech at constant stirring (500 ± 1) rpm, (25 ± 1) °C, solid-liquid ratio of 0.050, during (60 ± 1) min. The extraction of phenolic compounds using conventional solvents: H_2O, Ace, MeOH, EtOH, and a mixture of EtOH: H_2O (3:7) without and with pH control at pH 2 (by adding HCl at 1 mol/L) were also performed for comparison purposes. The pH of the solutions was measured using a METTLER TOLEDO SevenMulti pH meter within an uncertainty of ± 0.02. After extraction, the mixtures were centrifugated at 5000 rpm, 15 °C for 15 min. Supernatants were collected to separate the biomass from the extract. The supernatants were filtrated and stored at (4 ± 1) °C until analysis of the total phenolics and antioxidant capacity. All the experiments were executed protected from light since the phenolic

compounds are photosensitive. Each extraction was carried out in triplicate to determine the average content of phenolic compounds extracts and the respective standard deviation.

2.2.6. Phenolic compound assays

The total phenolic content (TPC) of kiwi extracts was determined by the Folin-Ciocalteu method, according to the methodology proposed by Koşar *et al.* [119] with modification. The absorbance was measured at 760 nm in a microplate reader. All analyses were carried out in UV-visible spectroscopy SYNERGY|HT microplate reader from BioTek. All analyses were carried out in triplicate and TPC was determined from a calibration curve previously established and by using gallic acid as the standard. The results were reported as milligrams of gallic acid equivalent per grams of dry weight of biomass (mg GAE/g DW).

2.2.7. Antioxidant assays

The antioxidant capacity of the extract was evaluated through measuring FRAP and ABTS free radical scavenging activities. The FRAP assay of the extracts was carried out according to Benzie *et al.* [120] with few modifications. The extracts were diluted up to 100 times in the correspondent solvent. The FRAP reagent prepared contained 300 mmol/L acetate buffer (pH 3.60), 10 mM TPTZ in 40 mmol/L HCl and 20 mmol/L $FeCl_3$ at a ratio of 10:1:1 (v/v/v). A volume of 10 µL of extract was mixed with 290 µL of FRAP reagent in a microplate, which was incubated for (30 ± 1) min at (37 ± 1) °C, in the absence of light. The absorbance was measured at 593 nm in a microplate reader. Trolox was used as standard to prepare the calibration curve to determine FRAP. Each experiment was repeated five times. The results were expressed in milligrams of trolox equivalent per gram of dry weight of biomass (mg TE/g DW).

The ABTS assay of the extracts was carried out according to Re *et al*. [121], with some modifications. Two stock solutions, 7 mmol/L ABTS solution and 2.45 mmol/L potassium persulfate solution, were mixed in a ratio of 1:1 (v/v), followed by the incubation for (16 ± 1) h at (25 ± 1) °C in the dark to react and produce the radical $ABTS^{\bullet}$. For the study of antioxidant activity, the $ABTS^{\bullet}$ solution was diluted with distilled H_2O to an absorbance of (0.70 ± 0.05) at 734 nm. The kiwi extracts were diluted up to 100 times in the correspondent solvent. Then, was added 280 µL of $ABTS^{\bullet}$ and 20 µL of each extract sample to a microplate. Blank (20 µL of diluted solvent, 280 µL $ABTS^{\bullet}$) and control of each sample (20 µL of diluted extract, 280 µL of distilled H_2O) was also prepared. The microplate was incubated in the dark for (30 ± 1) min at (25 ± 1) °C, and then the absorbance was recorded at 734 nm using a microplate reader. Each experiment

was repeated five times. The antioxidant activity (AA%) of the samples was calculated using the following equation:

$$\mathrm{AA\%} = 100 - \left(\frac{Abs_{sample} - Abs_{control}}{Abs_{blank}}\right) \times 100 \quad \text{(Equation 1)}$$

where, Abs_{sample}, Abs_{blank} and $Abs_{control}$ are the sample, control and blank absorbance values, respectively. The results were reported in milligrams of trolox equivalent per gram of dry weight of biomass (mg TE/g DW).

2.2.8. Design Mixture – Optimization of the solvent composition

Experimental planning for mixtures optimization to be used as extraction solvents is a valuable tool to study the synergistic or antagonistic effects of the components, and consequently to determine the optimum solvent composition [122]. The independent variables evaluated were H_2O, GVL and EtOH from 0 to 100 wt % using fourteen different assays (Table A.2.3, Appendix A.2). The extractions of phenolic compounds from kiwi peels were carried out in a carousel at the same conditions previously reported. Samples were centrifuged and the supernatant was collected, filtered and stored at (4 ± 1) °C until the determination of the response variables – TPC, FRAP and ABTS. All the experiments were carried out protected from light.

2.2.9. Response Surface Methodology (RSM) – Optimization of extraction conditions

The response surface methodology (RSM), such as the central composite design, is a multivariate statistical tool that was applied for optimization of the extraction conditions of phenolic compounds from kiwi peels. The relationship between the response and the independent variables was modelled according to this polynomial equation:

$$y = \beta 0 + \sum_{i=1}^{k} \beta i Xi + \sum_{i=1}^{k} \beta ii Xi^2 + \sum_{i<j}^{k} \beta i \beta j Xi Xj \quad \text{(Equation 2)}$$

where, $\beta 0$ represents the intercept or regression coefficient, βi, βii and βij are the linear, quadratic and interaction coefficients, Xi and Xj are the independent variables while k is the number of variables studied that can influence the response y. In this work, the independent variables were submitted to a factorial planning of 2^3 (3 variables, and 2 levels) to optimize the phenolic content and antioxidant activity, using the optimized solvent composition previously determined by the design of mixture (GVL:EtOH, 7:3 (wt/wt)). The function responses measured

were phenolic content (by TPC) and antioxidant activity of the extracts (by FRAP and ABTS assays), in order to maximize the phenolic compound content and the antioxidant activity of kiwi extracts. Twenty experiments were carried out and the conditions used are detailed in Appendix A.2 (Table A.2.4). The obtained results were statistically analyzed with a confidence level of 95 %. The significance of the models, as well as the lack-of-fit were evaluated by the analysis of variance (ANOVA). Coefficient of determination (R^2) and coefficient of determination adjusted (R^2_{adj}), and adequate precision were used to estimate the adequacy of the polynomial equation to the response. The experimental design, statistical analysis and regression model were executed using a Statistic Software Version 10.

In this work, 3 factorial planning were executed, each one by applying different techniques of extraction. The first factorial planning was a CE carried out in a Carousel Radleys Tech, where the temperature (T), extraction time (t) and solid-liquid ratio (S/L Ratio) were optimized. The 2^3 factorial planning used is described in Appendix A.2 (Table A.2.5). The second factorial planning was an ultrasonic UAE carried out in an ultrasonic processor (Branson, Digital Sonifier 450) with a maximal power of 400 W. In this factorial plan was varied the amplitude (Amp), extraction time and solid-liquid ratio; see conditions in Appendix A.2 (Table A.2.6). The third and last factorial planning corresponded to MAE done by Monowave 300 microwave synthesis reactor from Anton Paar. The variables investigated in this methodology were temperature, extraction time and solid-liquid ratio according to the experimental conditions evidenced in Appendix A.2 (Table A.2.7). After the extractions, all mixtures were centrifuged (conditions describe above) and the supernatants were filtered and stored at (4 ± 1) °C until the determination of total phenolic content (TPC) and the antioxidant activity assays (FRAP and ABTS). All the experiments were carried out protected from light.

2.2.10. Determination of the main phenolic compounds

Kiwi extracts were firstly filtered using PTFE filters with 0.2 µm pore diameter for ultra-high pressure liquid chromatography with ultraviolet detection mass spectrometric (UHPLC-UV-MS^n) analysis. Extracts (20 µL) were injected in the UHPLC system equipped with an Accela 600 LC pump, an Accela autosampler (set at 16 °C) and an Accela 80 Hz photo diode array detector (DAD) (Thermo Fisher Scientific, San Jose, CA, USA). The separation of extract components was developed in a Hypersil Gold RP C18 column (100 x 2.1 mm; 1.9 µm particle size) afforded by Thermo Fisher Scientific (San Jose, California, USA), preceded by a C18 pre-column (2.1 mm i.d.) supplied by Thermo Fisher Scientific (San Jose, CA, USA), and both were kept at 40 °C. The binary mobile phase included (A) water:acetonitrile (99:1, v/v) and (B) acetonitrile, both containing

0.1% (v/v) formic acid. A gradient elution program was applied at a flow rate of 0.40 mL/min for 32 min, as follows: 1 % B kept from 0 to 1 min; 1-4 % B from 1 to 3 min; 4-27 % B from 3 to 17 min; 27-46 % B from 17 to 19 min and 46-100 % B from 19 to 22 min. Before the next run, the B percentage was reduced from 100 to 1 % for 4 min, and then kept at 1 % B for 4 min. The chromatograms were recorded at 280 and 350 nm, and the molecular absorption spectra between 210 and 600 nm.

The UHPLC system was coupled to a LCQ Fleet ion trap mass spectrometer (Thermo Finnigan, San Jose, CA, USA) equipped with an electrospray ionization (ESI) source. The ESI-MS was operated under the negative ionization mode with a spray voltage of 5 kV and capillary temperature of 320 °C. The flow rate of nitrogen sheath and auxiliary gas were 40 and 5 (arbitrary units), respectively. The capillary and tube lens voltages were set at -44 and -225 V, respectively. Collision induced dissociation-MSn experiments were executed on mass-selected precursor ions in the range of m/z 100-2000. The isolation width of precursor ions was 1.0 mass units. The scan time was 100 ms and the collision energy was 35 arbitrary units, using helium as collision gas. The data acquisition was carried out using Xcalibur® data system (Thermo Finnigan, San Jose, CA, USA).

3. Results and Discussion

3.1. Hydrotropy study

3.1.1. Hydrotropic effect of biobased solvents

The solubility of ferulic acid, syringic acid and catechin in aqueous solutions of biobased solvents (GVL, CYR, PRO and HEX) was measured in this work. The solubility of these three phenolic compounds was determined over the entire possible hydrotrope concentration range, *i.e.*, from pure water to pure biobased solvent or its aqueous solubility limit.

The solubilities measured for ferulic acid, syringic acid and catechin in pure water at 30 °C, were (0.83 ± 0.05) g/L, (1.48 ± 0.03) g/L and (8.6 ± 0.3) g/L, respectively. They are in fair agreement with the data reported in the literature for ferulic acid (0.92 g/L at 30 °C) [123] and syringic acid (1.43 g/L at 30 °C) [124], with few deviations for the catechin (3.80 g/L at 35 °C) [125]. The obtained solubility curves are presented in Figure 8 and the detailed experimental data can be found in the Appendix B.1 (see Table B.1.1, B.1.2 and B.1.3). The results obtained are shown as solubility enhancement, S/S_0, where S and S_0 represent the solubility of phenolic compounds in each biobased aqueous solution and in pure water, respectively. Note that, the solubility values of (+)-catechin are presented in mole fraction of (+)-catechin anhydrate. Since water solubility of compounds can be affected by the pH, the starting and final pH of all solutions were assessed to infer some interferences caused by changes in the solute charge (see Table B.1.4-B.1.7, Appendix B.1). In terms of solute speciation, all saturated solutions (including those in pure water) have pH values mostly below the first pKa value of ferulic acid (pKa$_1$= 3.58) [126], syringic acid (pKa$_1$= 3.93) [126], and catechin (pKa$_1$= 9.00) [126]. More specifically, catechin was completely in the neutral form for all hydrotrope solutions, whereas for ferulic acid and syringic acid they were 51% and 57% in the neutral form, respectively; except for the pair ferulic acid and aqueous 1,6-hexanediol solutions at higher concentrations, where only 30% of ferulic acid was in the neutral form.

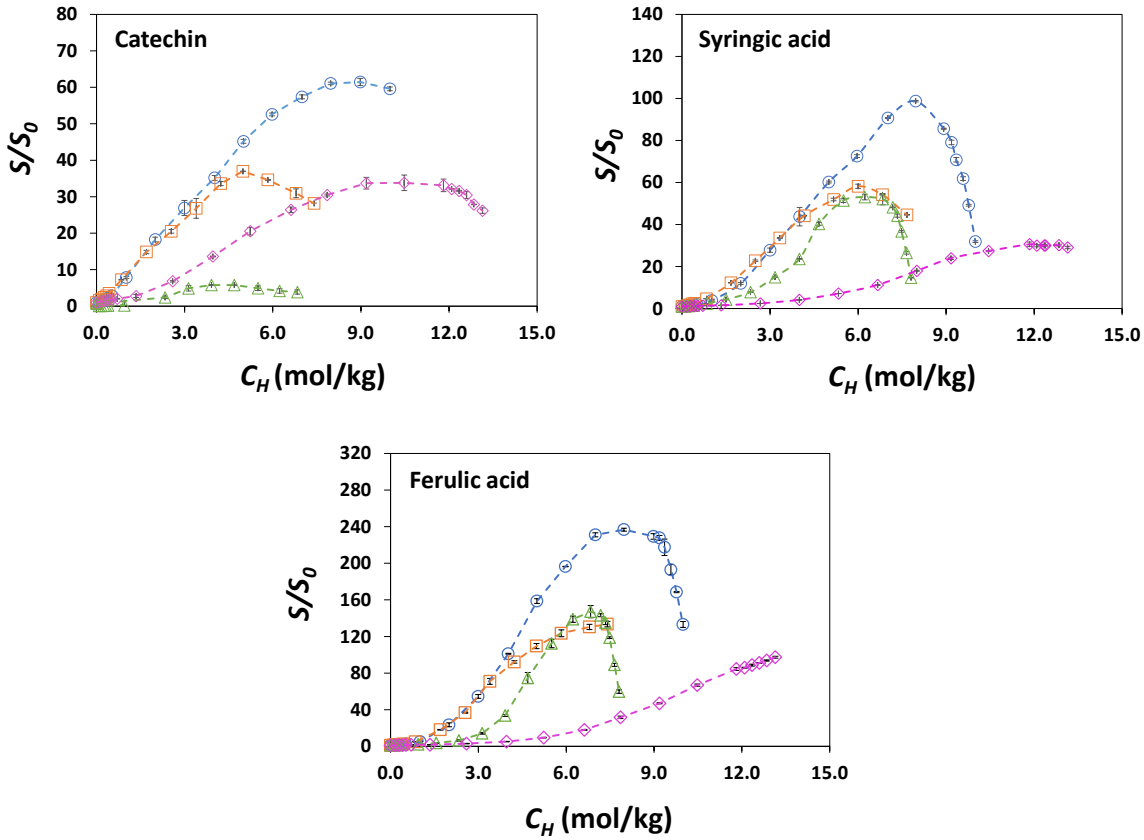

Figure 8. Solubility enhancement (S/S_0) for catechin, syringic acid and ferulic acid in aqueous solutions of biobased solvents: GVL (●), HEX (■), CYR (▲) and PRO (◆) as a function of hydrotrope concentration (C_H) at 30 °C. S and S_0 represent the solubility of the solute in aqueous solutions of biobased solvents (hydrotrope) and in pure water, respectively. The dashed lines are visual guides.

The ability of biobased solvents to enhance the aqueous solubility of ferulic acid, syringic acid and catechin is remarkable, as expressed in Figure 8. Choosing the value of 6.0 mol/kg as a metric of interest, in general, the best biobased solvent to enhance the solubility of phenolic compounds increases in the following order: PRO < CYR < HEX < GVL. Most solubility curves depicted in Figure 8 pass through a maximum (*e.g.,* ferulic acid/GVL and syringic acid/GVL systems), most likely related to the transition between "biobased solvent in water" to "water in biobased solvent" and a change in the solvation mechanism. A typical hydrotropy solubility curve presents a sigmoidal shape, and this shape is observed for most of the systems in this study. The system CYR/catechin was the only one that did not seem to have a hydrotropic behavior with the catechin, therefore this pair was not evaluated in the following studies. Outstanding results on the solubility of the phenolic compounds were obtained for the aqueous solutions of GVL, leading to increments up to 61-fold, 99-fold, 237-fold for catechin, syringic acid and ferulic acid when compared to pure water, respectively. These results are in line with the

expectations of Kerkel *et al.* [87], who proposed GVL as a promising "green" solubilizer for pharmaceutical, cosmetic and agrochemical compounds. Moreover, the aqueous solubility increase of syringic acid using CYR, previously studied, was up to 45-fold [116] similar to that obtained in this study, which was up to 53-fold. Furthermore, the linear (alkanediols) or cyclic (GVL and CYR) structure of biobased solvents seems not to directly correlate with their ability to solubilize phenolic compounds, since no apparent effects related to the structure (linear or cyclic) on the solubilization of these compounds could be observed. This will be discussed in the following sections.

In relation to the individual analysis of the hydrotopes, it has been suggested that most hydrophobic hydrotropes, having fewer interactions with water, would be more available to interact with solutes and increase their solubility in water [127]. We used here the logarithm of the octanol-water partition coefficients log (K_{OW}) as a measure of the hydrophobicity of the solvents (see Table 6) and this behavior was not observed for any pair solute/hydrotrope in this study. Looking at the individual solubility curves of each solute, it can be observed that the behaviors and trends depend on the concentration and structure of biobased solvents. Figure 8 is organized from the most hydrophilic (catechin) to the most hydrophobic (ferulic acid) solute for an easier interpretation. The log *(*K_{OW}) of the solutes is presented in Table 6. Catechin has a large structure (with 3 rings) but also many hydroxyl groups (5 groups), making it very hydrophilic when compared to the other compounds. The ferulic acid has a higher hydrophobicity and a higher solubility enhancement compared to syringic acid and catechin, highlighting the tendency of hydrotropes to increase solubility according to the hydrophobicity of solutes, as previously reported in the literature [117]. Our results seem thus to be in agreement with the recently proposed molecular mechanism of hydrotropy, [111], *i.e.,* hydrotropy is driven by the apolarity of both the hydrotrope and the solute, whereas the best hydrotropes have identical apolarity to the solute.

Table 6. Maximum solubility enhancement ($(S/S_0)_{max}$) attained for ferulic acid, catechin and syringic acid in aqueous solutions of biobased solvents along with the logarithm of the octanol-water partition coefficient, log (K_{OW}), of both solutes and hydrotropes [128].

	log (*K*ow)	HEX	GVL	CYR	PRO
Catechin	0.58	36.97 ± 0.01	61 ± 1	4.8 ± 0.1	34 ± 2
Syringic acid	1.04	58 ± 1	98.7 ± 0.3	53 ± 1	31 ± 1
Ferulic acid	1.51	133 ± 3	237 ± 2	147.2 ± 7	97 ± 1
	log (*K*ow)	-0.07	-0.27	-0.71	-1.34

3.1.2. Analysis of hydrotropy in diluted solutions by the Setschenow constants

The understanding of the biobased solvent structure effect (cyclic or linear) in the molecular mechanism of hydrotropy it is clearly challenging when considering the multiple interactions that can occur between the three components present in the solution (hydrotrope, water and solute). All of them have significant functions (greater or minor) in the solubility enhancement of the solute. While this is true at high concentrations of hydrotrope and solute, in the diluted region the interactions between solute-solute and hydrotrope-hydrotrope should decrease significantly. Thus, the analysis of the diluted region is also important for a better understand of the interaction hydrotrope-solute.

Hence, to the evaluation of diluted region, the Setschenow constant was determined [110]. According to the definition, the Setschenow constant quantifies the change in the solubility of a solute due to the presence of a hydrotrope in the dilute region which is represented by the equation (3) [110]:

$$\ln(S/S_0) = C_H \,.\, K_S \qquad \text{(Equation 3)}$$

where, S and S_0 represents the solute solubility (mol/L) in the hydrotrope solution and pure water, respectively; C_H represents the concentration of hydrotrope (mol/kg), and K_S represents the Setschenow constant (kg/mol). The Setschenow constant equation is only valid in a concentration region for which the variation of the natural logarithm of solute solubility remains linear. In this work this range was found to be up to about 20 wt %, depending on the hydrotrope.

The Setschenow constants for all solute-hydrotrope pairs here studied were calculated and the obtained results are reported in Table 7 (see Figure B.1.1, B.1.2 and B.1.3 in Appendix B.1), along with the weight percentage (wt %) range used. The values of the constant give

information about the efficiency of the hydrotrope in the solubilization of a specific solute. The higher the values of K_S, the higher is the ability of the hydrotrope to increase the solute solubility in water. Remarkably, the values of K_S, describing the low concentrated region, seem to contradict the results obtained in the initial qualitative assessment of the solubility curves presented in Figure 8. Comparing the results of solubility and the values of K_S determined, it is possible to observe that the hydrotropic capacity of biobased solvents, in the dilute region does not follow the same tendency observed for at concentrated solutions, since there are multiple interactions that difficult the interpretation of results, as it was explained before. For example, for all solutes, HEX presents the highest Setschenow constant values and the higher hydrophobicity (log(K_{OW}) = -0.07), as can be seen in Figure 9; however, GVL is the biobased solvent with the maximum values of $(S/S_0)_{max}$ (*cf.* Table 6), still presents the lowest hydrotropic constants and hydrophobicity (Figure 9). According to the values of K_S obtained, hydrotropic power of biobased solvents follows the order: HEX > GVL > CYR > PRO, which correlate well with the hydrophobicity of each hydrotrope (Figure 9). This reinforces the theory recently proposed [111], suggesting that the larger the apolar volume of the hydrotrope, the larger the solubility enhancement in the diluted region. Thus, the results here obtained prove the importance to evaluate the diluted region, since this allows a better understanding of the molecular mechanism of hydrotropy.

Table 7. Setschenow constants (K_S) for catechin, syringic and ferulic acids in biobased solvents, and the hydrotrope concentration range considered in the calculations.

	K_S (kg/mol)	Concentration range (wt %)
Catechin		
HEX	3.158	0-5
GVL	2.030	0-10
CYR	---	---
PRO	1.111	0-5
Syringic acid		
HEX	1.939	0-10
GVL	1.287	0-20
CYR	0.964	0-20
PRO	0.352	0-20
Ferulic acid		
HEX	1.956	0-10
GVL	1.600	0-20
CYR	1.444	0-5
PRO	0.697	0-5

*CYR has no hydrotropic effect with catechin.

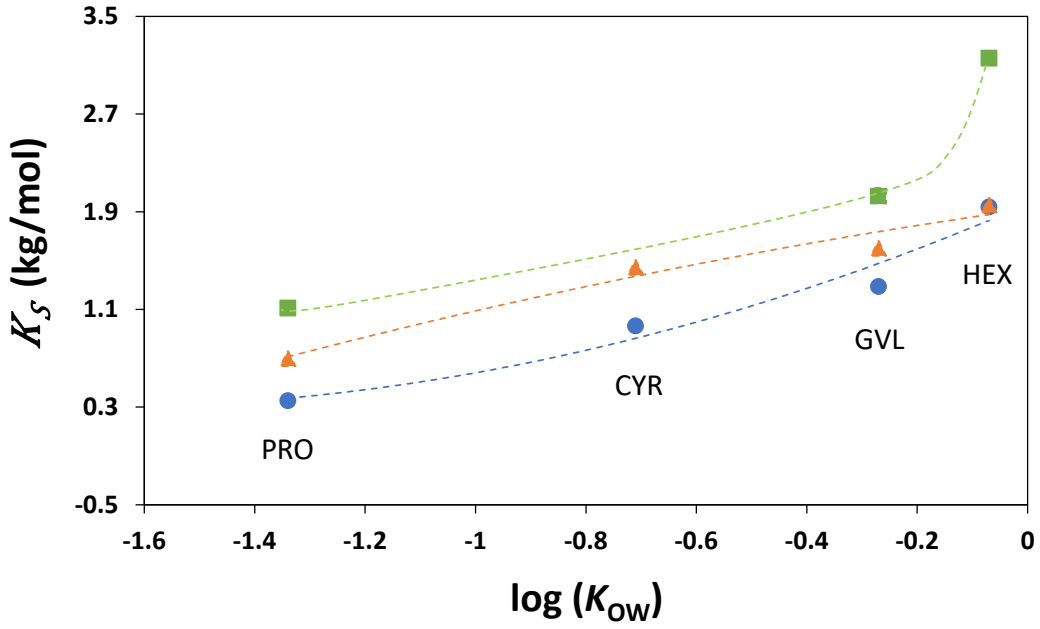

Figure 9. Representation of K_S as a function of the logarithm of octanol-water partition coefficient of hydrotropes, log (K_{OW}) for syringic acid (●), ferulic acid (▲) and catechin (■).

The Setschenow constant is related to Kirkwood–Buff Integrals (KBI), through the expression below [129]:

$$K_S \propto G_{S,H} - G_{S,W} \qquad \text{(Equation 4)}$$

The KBI measure the excess of a component present in the local vicinity of another component. Therefore, $G_{S,H}$ and $G_{S,W}$ quantify the excess of hydrotrope or water around the solute, respectively. Thus, the higher the Setschenow constant, the higher will be the preference of the solute to interact with the hydrotrope, and not with water, and so the solubility enhancement of solute should be higher. This is the reason why the hydrophobicity drives the hydrotropy. A solute with higher hydrophobicity increases the probability of a hydrotrope-solute pair to form and, consequently, increases the K_S. However, this is not in agreement with our data, since the solute with higher hydrophobicity, which is ferulic acid (log(K_{OW}) = 1.51), has a lower K_S for the same hydrotrope, than catechin and similar to syringic acid (log(K_{OW}) = 0.58 and 1.04, respectively). As referred before, the increase of hydrotrope hydrophobicity leads to a higher interaction with the solute and a consequent increase of K_S. This is verified on the results present in Tables 6 and 7. However, it seems that, despite the significant impact of hydrotrope hydrophobicity on the hydrotropy at diluted region, solute hydrophobicity has no influence. The understanding of the nature of this tendency on solutes will be the object of a future work.

3.1.3. Analysis of hydrotropy in concentrated solutions by the cooperative model

To better understand hydrotropy mechanism, the cooperative model of hydrotropy developed by Shimizu and Matubayasi [130] was used here. This recent statistical thermodynamic theory clarifies the origin of cooperative phenomena by using an approximation in the description of hydrotropy, characterized by sigmoidal curves, and the interaction phenomenon between solute and hydrotrope. This model is capable to express the solubility as a function of hydrotrope concentration, by the following equation:

$$\ln\left[\frac{1-\frac{S}{S_0}}{\frac{S}{S_0}-\left(\frac{S}{S_0}\right)_{max}}\right] = m\ln\left(x_H\right) + b \qquad \text{(Equation 5)}$$

where *S* represents the molar solubility (mol/L) of the solute in the hydrotropic system, S_0 is the molar solubility (mol/L) of the solute in pure water, $(S/S_0)_{max}$ is the maximum attainable relative solubility, *i.e.,* the value of the plateau in the sigmoidal solubility curve, and x_H is the mole fraction of the hydrotrope in the ternary mixture, water-hydrotrope-solute system, after the saturation. The parameters *m* and *b* give us a better insight into the model relative to the interactions between hydrotrope and solute. They are obtained directly from the linearized curve as the slope and intercept, respectively. The parameter *m* represents the number of hydrotrope molecules around the solute, and *b* corresponds to the facility to insert that number (*m*) of hydrotrope molecules in the volume corresponding around to the solute.

This model was used to fit catechin, syringic and ferulic acids solubility curves studied in this work. It is important to refer that hydrotrope concentrations expressed as mol/kg in the previous section, were converted in mole fraction (mol/mol). The results presented in Figure 10 demonstrate the ability of the model to describe the solubility curves of catechin, syringic and ferulic acids in the presence of aqueous solutions of biobased solvents, being the linearized equation represented in Appendix B.1 (Figures B.1.4-B.1.6). The parameter $(S/S_0)_{max}$ of equation 5 was fitted as an adjustable parameter (ranging from the experimental $(S/S_0)_{max}$ to an infinite value) since most of the solubility curves are not perfectly sigmoidal and some of them have an absolute maximum, being difficult to ascertain the maximum value.

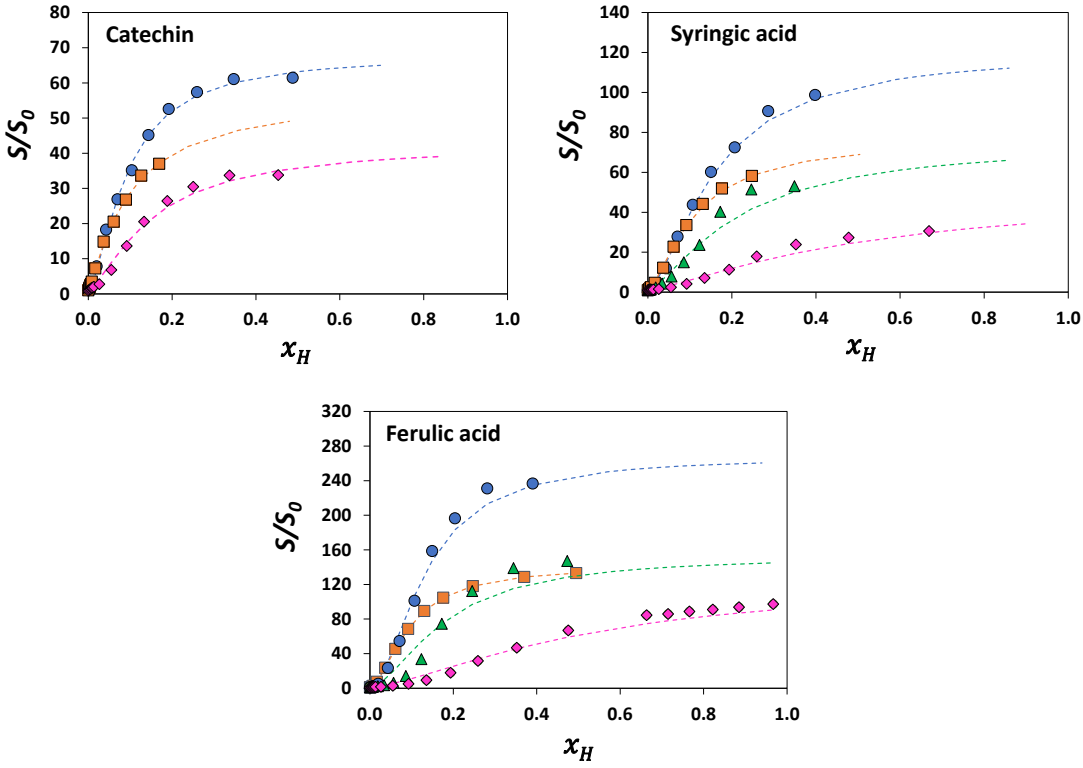

Figure 10. Representation of the cooperative model to fit the solubility curve (sigmoidal curve) of catechin, syringic and ferulic acid in the presence of aqueous solutions of biobased solvents: GVL (●), HEX (■), CYR (▲) and PRO (◆) as a function of hydrotrope mole fraction (x_H) at 30 °C.

According to the actual understanding of the hydrotropy mechanism, the maximum displayed by some of the solubility curves is due to a change in the solvation around the solute. The system moves from a hydrotrope driven solvation in water, to a water driven solvation in the hydrotrope. Beyond the $(S/S_0)_{max}$, which is reached at high hydrotrope concentrations, the component water is no longer the major solvent, and thus water-mediated hydrotrope-solute interactions are no longer predominant in the system. This results in the transition of an hydrotropy environment to a co-solvency regime [117]. The experimental data used for the linearized plot is only applied until the maximum solubility (Figures B.1.4-B.1.6, Appendix B.1,) as the cooperative model of Shimizu [111] is not applicable beyond this point.

The correlation parameters obtained for all solubility curves are shown in Table 8. The parameter *m* present in equation 5 of the cooperative model of hydrotropy represents the number of hydrotrope molecules around the solute. Analyzing all the model parameters from Table 8 and Figure 11 it can be seen a specific pattern between log (K_{OW}) and the parameter *m.*

Table 8. Parameters acquire from the cooperative model of hydrotropy by using the experimental data collect in this work.

		Shimuzu			
		HEX	GVL	CYR	PRO
Catechin	*m*	1.18	1.55	---	1.38
	b	2.71	3.70	---	2.53
Syringic acid	*m*	1.48	1.54	1.35	1.25
	b	3.24	2.71	1.82	0.56
Ferulic acid	*m*	1.67	1.84	1.69	1.21
	b	3.79	3.69	2.90	0.16

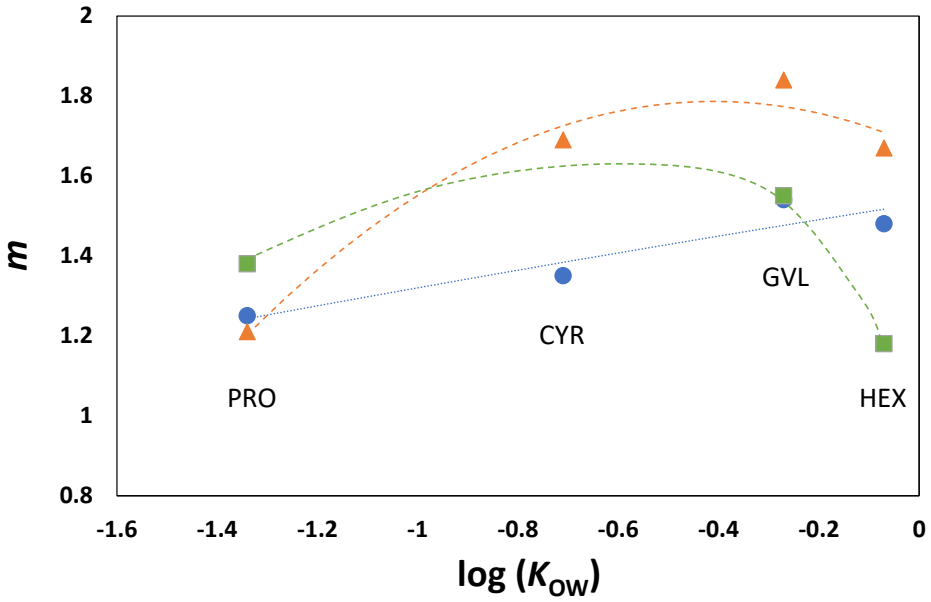

Figure 11. Parameter *m* of the cooperative model of hydrotropy as a function of the logarithm of octanol-water partition coefficient of hydrotropes, log (K_{OW}) for syringic acid (●), ferulic acid (▲) and catechin (■).

Ferulic acid has a higher hydrophobicity, thus it would be expected to be surrounded by a higher number of hydrotropes, and so the parameter *m* should be higher. In fact, this is observed. Ferulic acid has a higher parameter *m* when compared to the other solutes: *m* (ferulic acid) > *m* (syringic acid) > *m* (catechin) for HEX, GVL and CYR, with exception of PRO (Figure 11). This relation between *m* and solute log(K_{OW}) was previously demonstrated [110,116]. The number of hydrotrope molecules around the solute is related to the preference of the solute to be surrounded by a hydrophobic medium, reaching a maximum when the apolarity of both

solute and hydrotrope are equal. As shown in Figure 11 a maximum is achieved for catechin and ferulic acid. After this point hydrotrope-hydrotrope aggregation becomes larger, compared to the solute-hydrotrope interactions and, consequently there is a tendency to decrease.

Despite the overview of hydrotropic effect at hydrotrope dilute and concentrate regions, it is still difficult to ascertain what happens in the different regions that explain why hydrotropes of higher hydrophobicity - such as HEX - performs better at lower concentrations and is surpassed by less hydrophobic hydrotropes - such as GVL - at higher concentrations. The differences observed between these hydrotropes could be related with the interactions established in the different regions: hydrotrope-hydrotrope interactions should prevail instead hydrotrope-solute interactions at hydrotrope concentrated region. Since HEX has a higher hydrophobicity, at higher concentrations hydrotrope-hydrotrope interactions become larger than hydrotrope-solute interactions, and so their action in solubility enhancement decreases. For GVL that presents a lower hydrophobicity, the interactions between hydrotropes are less predominant and thus solubility enhancement is higher than that induced by HEX. On the other hand, at hydrotrope lower concentrations, the interactions between hydrotrope-solute should be predominant and HEX performance is better than GVL, in accordance with the Setschenow constant, and as established in the recent proposed theory [116]. Additionally, according to a study, which evaluates the alkyl chain length of ethyl glycerol's, they demonstrate that the higher is hydrophobicity (the higher the alkyl chain length), the better is the hydrotropy constant at lower concentrations [110]. Additionally, the hydrotrope with the higher alkyl chain length loss influence in the concentrated region [110]. The results obtained here for the alkanediols (HEX in relation to PRO), correlate with those results.

3.1.4. Solubility of phenolic compounds at high pressure

Solubility tests at high pressure were made in order to understand if pressure could have a positive effect in the solubility of phenolic compounds in aqueous solutions. These experiments were done using the best hydrotrope-solute pair: the system composed of GVL and ferulic acid. These experiments were carried out in pressure cells at normal pressure (1 bar) and high pressure (100 bar). The results are presented in Figure 12 (Table B.1.8, Appendix B.1) and were compared to those obtained when using the thermomixer and GVL aqueous solutions at 10 wt %, 30 wt % and 50 wt %.

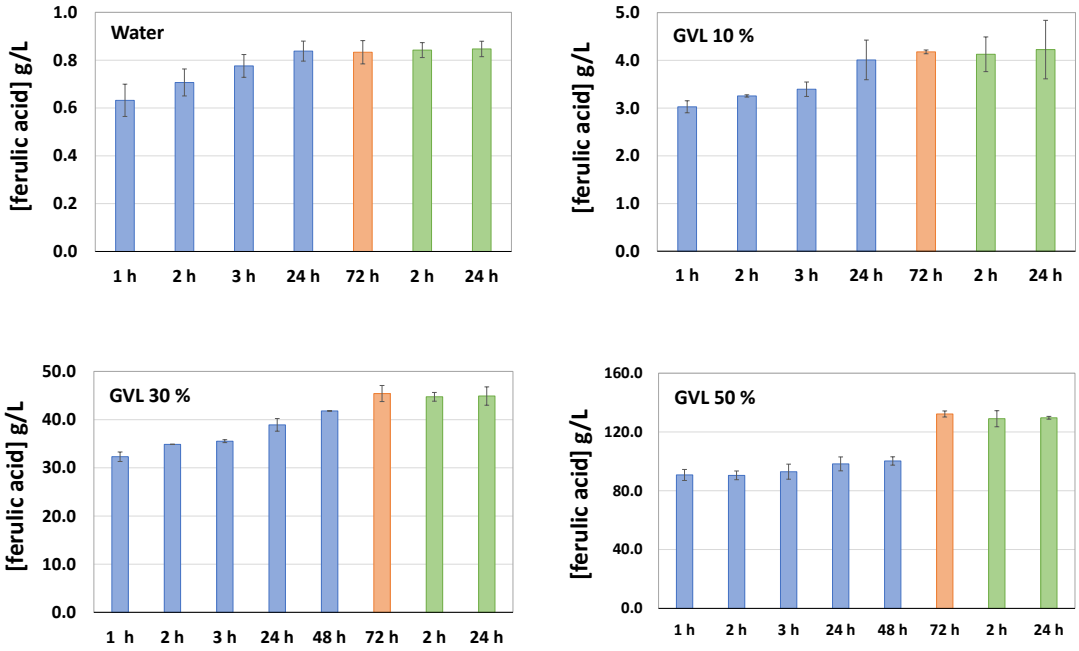

Figure 12. Ferulic acid solubility in GVL aqueous solutions (0 %, 10 %, 30 % and 50 % of GVL) at normal pressure (1 bar) at 30 °C by using cells (blue bars) or thermomixer (orange bars) and at high pressure (100 bar, green bars).

By the comparison of the results obtained at normal pressure in cells and thermomixer, it is possible to conclude that, as GVL concentration increases, the time needed to reach the saturation inside cells is higher. However, when high pressure is applied, despite no better results are observed for ferulic acid solubility when compared to thermomixer experimental results, saturation happens at very short times, with 2h being enough to reach the same saturation value.

3.1.5. Conclusions

The solubility of hydrophobic compounds, including catechin, syringic acid and ferulic acid was evaluated in aqueous solutions of biobased solvents. In general, all solvents presented a good hydrotropic effect. According to the solubility curves, the best biobased solvent was GVL, since it demonstrated a higher $(S/S_0)_{max}$: up to 237-fold for ferulic acid, up to 99-fold for syringic acid and up to 61-fold for catechin. The evaluation of Setschenow constant demonstrated that hydrotrope hydrophobicity plays an important role in the mechanism of hydrotropy at hydrotrope dilute concentration region. Moreover, the cooperative hydrotropy model was applied to fit the experimental data measured in this work. The parameters obtained were analyzed in terms of physical meaning and it was verified a relation between the parameter *m* and hydrotrope log(K_{OW}), as previously reported in literature. To sum up, at low hydrotrope

concentrations, hydrotropes of higher hydrophobicity (*e.g.* HEX) perform better than less hydrophobic hydrotropes (*e.g.* GVL), being surpassed at higher concentrations by the same ones. This is explained by hydrotrope-hydrotrope interactions being predominant at concentrated region for more hydrophobic solvents, and thus their hydrotropic effect over the solute decreases. On the other hand, the hydrophobicity of the solute has a more significant role in the solubility enhancement for the concentrated regions, being object of a future work. Finally, this work showed that aqueous solutions of biobased solvents are great hydrotropes, some of which had not yet been identified, only CYR. Thus, it is important to choose an hydrotrope, its concentration, hydrophobicity variable, and solute properties to increase solubility for a determined application.

Solubility tests at high pressure were carried out by using the best hydrotrope-solute pair, composed by GVL and ferulic acid to understand if pressure has a positive effect on the solubility enhancement. The results showed that ferulic acid solubilization at high pressure is not enhanced, still the saturation occurred in a shorter time, reducing the solubilization time from 72 h to 2 h.

3.2. Extraction of phenolic compounds from kiwi waste

3.2.1. Biomass collection, selection and storage

Kiwi peel, pulp and juice present different levels of phenolic compounds and antioxidant activity as mentioned above. Thus, was studied the phenolic content of the different parts of kiwi – peel, pulp (including seeds) and juice individually or the whole kiwi, being the last used for comparison purposes. The polyphenols content (TPC) and the antioxidant activity (FRAP and ABTS) were determined for each sample. The results obtained for TPC, FRAP and ABTS follow the order: peels > whole fruit > pulp > juice (*cf.* Table A.2.1 and Figure A.2.1, Appendix A.2). Therefore, kiwi peels were identified and selected as the most promising kiwi residue to be used on the extraction of phenolic compounds. All remaining experiments of this work were carried out by using kiwi peels.

The influence of different storage conditions (biomass dried at room temperature and stored at -10 °C, biomass stored directly at -10 °C and -80 °C) on the phenolic content of the selected biomass (peels) was investigated. The results obtained for TPC, FRAP and ABTS follow the order: biomass directly stored at -80 °C > biomass directly stored at -10 °C >> biomass dry and stored at -10 °C. Thus, the results obtained showed that storing the kiwi directly at -80 °C is the most efficient way to protect the phenolic content of the kiwi peels (*cf.* Table A.2.2 and Figure A.2.2, Appendix A.2).

3.2.2. Screening of biobased solvents for the extraction of phenolic compounds

Several mixtures of biobased solvents (biobased solvent + H_2O, biobased solvent + EtOH and biobased solvent + EtOH + H_2O) were investigated to infer on their ability to extract phenolic compounds from kiwi peels. The results obtained are presented in Figure 13 (detailed experimental data are provided in the Table B.2.1 in Appendix B.2). The antioxidant activity of the solvents used in the extractions was confirmed to be negligible. Furthermore, two antioxidant activity assays were performed (FRAP and ABTS), since the use of a single assay may not reflect the total antioxidant capacity of a given sample. Each of the implemented assays uses a different type of oxidizing agent, that is affected differently by conditions such as the nature of the compounds present in the matrix, the pH of the solution, etc [131]. Therefore, the combination of different methodologies to evaluate the antioxidant activity of the extracts is important.

As shown in Figure 13, the extracts obtained with mixtures of biobased solvents present higher levels of phenolic content and antioxidant activity than those obtained with conventional solvents. Biobased solvent mixtures of CYR were the only exception, showing to have

antioxidant activity, perhaps due to the aromatic ring present in its structure. Thus, the extracts obtained with CYR could not be quantified by any of the methods studied (TPC, FRAP and ABTS) and so are not evidenced in the Figure 13. The binary and ternary mixtures composed of GVL and ETG (in the ratio of 7:3 (wt/wt) and 4:4:2 (wt/wt) showed to be the best options for the extraction of phenolic compounds, with GVL:EtOH in the ratio of 7:3 (wt/wt) leading to the highest extraction yield of TPC (19 ± 1) mg GAE/g DW and antioxidant properties: FRAP (47 ± 1) mg TE/g DW and ABTS (70 ± 2) mg TE/g DW. Considering the mixtures based on alkanediols, the mixtures with ETG lead to extracts with higher amounts of phenolic compounds and higher antioxidant activity than the others under study (PRO and HEX). These results can be explained by the effect of alkanediol alkyl chain length and, consequently, the polarity of the solvent. ETG presents a more polar structure in comparison to PRO and HEX, since it has a shorter alkyl chain, which seems to facilitate the interaction between the phenolic compounds and the biobased solvent, as previously observed by Alañón *et al.* [132]. The authors analyzed the extraction of phenolic compounds from olive leafs using deep eutectic solvents (DES). It was demonstrated that choline chloride-ETG was the most effective DES, due to its polarity and linear structure compared to choline chloride-PRO or choline chloride-xylitol, respectively. However, looking at Figure 13, it is possible to verify that the extracts obtained using mixtures composed of water and HEX showed a slightly higher phenolic content and antioxidant activity than the extracts obtained with PRO. This behavior is not in agreement with the trend reported by Alañón *et al.* [132], and further studies are needed to better understand the alkyl chain length effect on phenolic compounds extraction in aqueous mixtures.

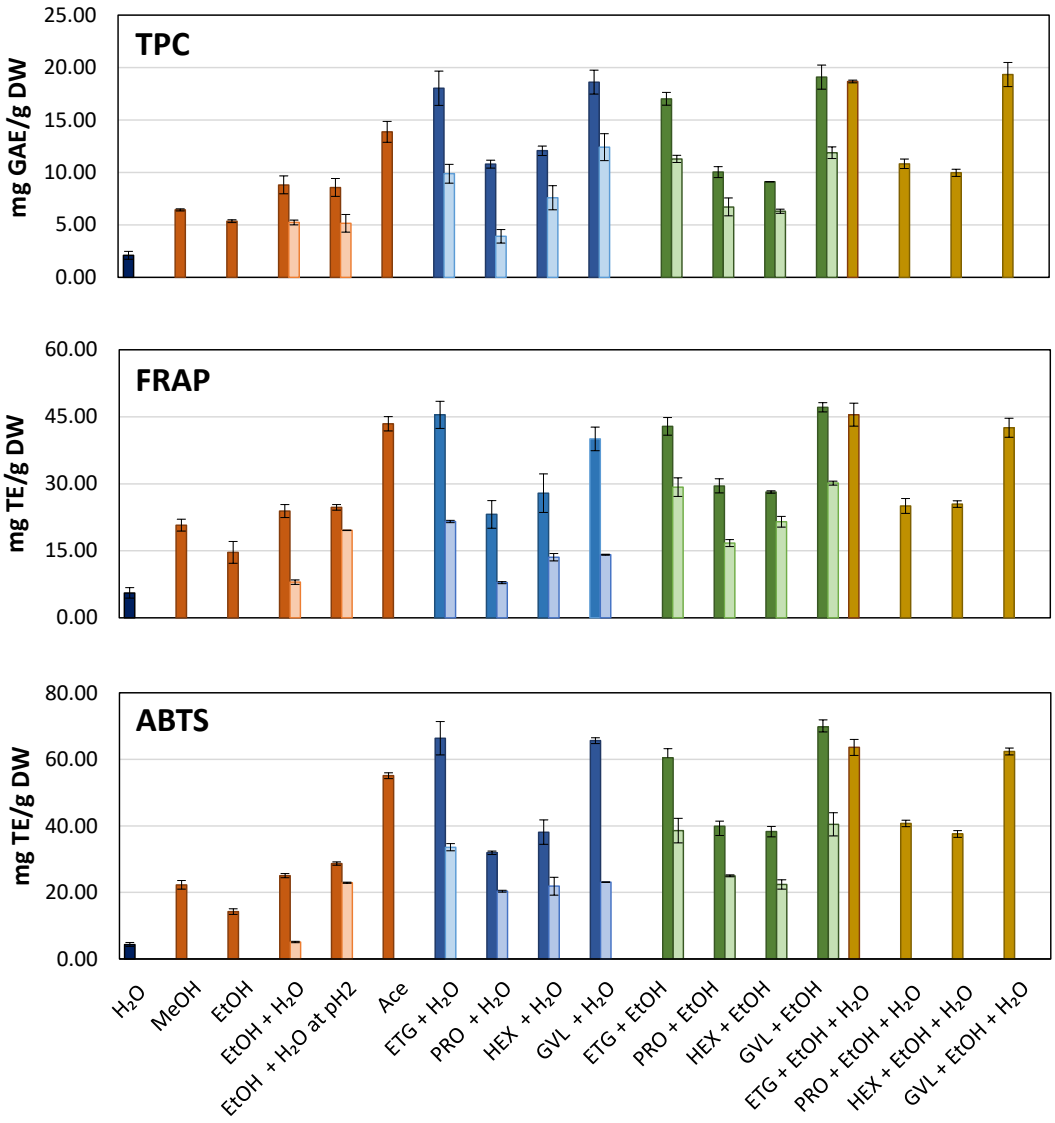

Figure 13. Evaluation of the phenolic content (TPC) and the antioxidant activity (FRAP and ABTS) of kiwi peels extracts obtained by using conventional solvents (orange), binary mixtures of biobased solvents with H_2O (blue) or EtOH (green) in a ratio of 3:7 (wt/wt, dark color) and 7:3 (wt/wt, light color), and ternary mixtures composed of biobased solvent, EtOH and H_2O in a ratio of 4:4:2 (wt/wt, brown). Solvent's nomenclature can be found in Table 5. Fixed extraction conditions: CE, solid-liquid ratio of 0.050, 25 °C, 60 min.

Ace was the only conventional solvent that presented better results than some biobased solvent mixtures (*e.g.* mixtures composed of PRO and HEX) – *cf.* Figure 13. The high efficiency of Ace when compared with other conventional solvents in the extraction of phenolics compounds was in accordance with the results obtained by Zeinab *et al*. [36], where the extracts obtained with Ace also showed the highest phenolic compound content (24.5 ± 0.2) mg GAE/g DW. However, it should be taken into account that Ace high efficiency, in comparison to the other

conventional solvents, can be explained by the facility to extract other strong antioxidant compounds such as carotenoids, lutein, vitamin C and chlorophylls, as reported by Cassano *et al.* [133].

Concerning the pH effect in the extraction of phenolic compounds, this was negligible as shown in Figure 13 (Tables B.2.1 and B.2.2 in Appendix B.2). For instance, EtOH: H_2O (7:3, wt/wt) without pH control (pH = 8.08) have similar phenolic content and antioxidant activity – TPC = (8.8 ± 0.9) mg GAE/g DW, FRAP = (24 ± 1) mg TE/g DW; ABTS = (25.0 ± 0.6) mg TE/g DW – to EtOH: H_2O mixture (7:3, wt/wt) at pH 2 – TPC = (8.6 ± 0.9) mg GAE/g DW; FRAP = (24.7 ± 0.6) mg TE/g DW; ABTS = (28.7 ± 0.5) mg TE/g DW. However, these results are not in accordance with experimental data previously reported by Aires *et al*. [67]. In this work, authors observed that EtOH:H_2O (7:3, wt/wt) mixtures at pH 2 allowed to obtained extracts from kiwi pomace with higher phenolic content and antioxidant activities [67]. The differences observed between the results reported by Aires *et al*. [67] and this work can be related with the different types of biomass under evaluation: kiwi peel *vs.* pomace. As previously referred, each part of the kiwi has different levels and types of phenolic compounds [38], which present different solubilization properties in the extraction medium [134].

3.2.3. Optimization of the solvent composition

Considering the abovementioned results, the mixtures composed of ETG and GVL are the best to obtain extracts with higher phenolic content and antioxidant activity (*cf.* Figure 14). However, according to US Food and Drug Administration (FDA), ETG belongs to Residual Solvents Class 2, which means their use should be limited in pharmaceutical products due to their inherent toxicity [71]. On the other hand, GVL can be found naturally in fruits [83], and due to their non-toxic and non-volatile characteristics, is a compound frequently used as a food additive [83,91]. Moreover, GVL and their mixtures have not been used to extract bioactive compounds from biomass so far, highlighting the novelty of this work. Based on its favorable properties, a ternary mixture design using GVL, combined with EtOH and H_2O, was carried out in order to find the best solvent composition to obtain an extract with the highest phenolic content and antioxidant activity - Figure 14. All analyses were carried out with a confidence level of 95 % using the statistical model analysis variance (ANOVA) shown in Appendix B.2 (Figures B.2.1 and B.2.2). The experimental and predicted results were very similar, supporting the adequability of the statistical model (all analyses present an $R^2 > 0.90$ and $R^2_{adj} > 0.84$).

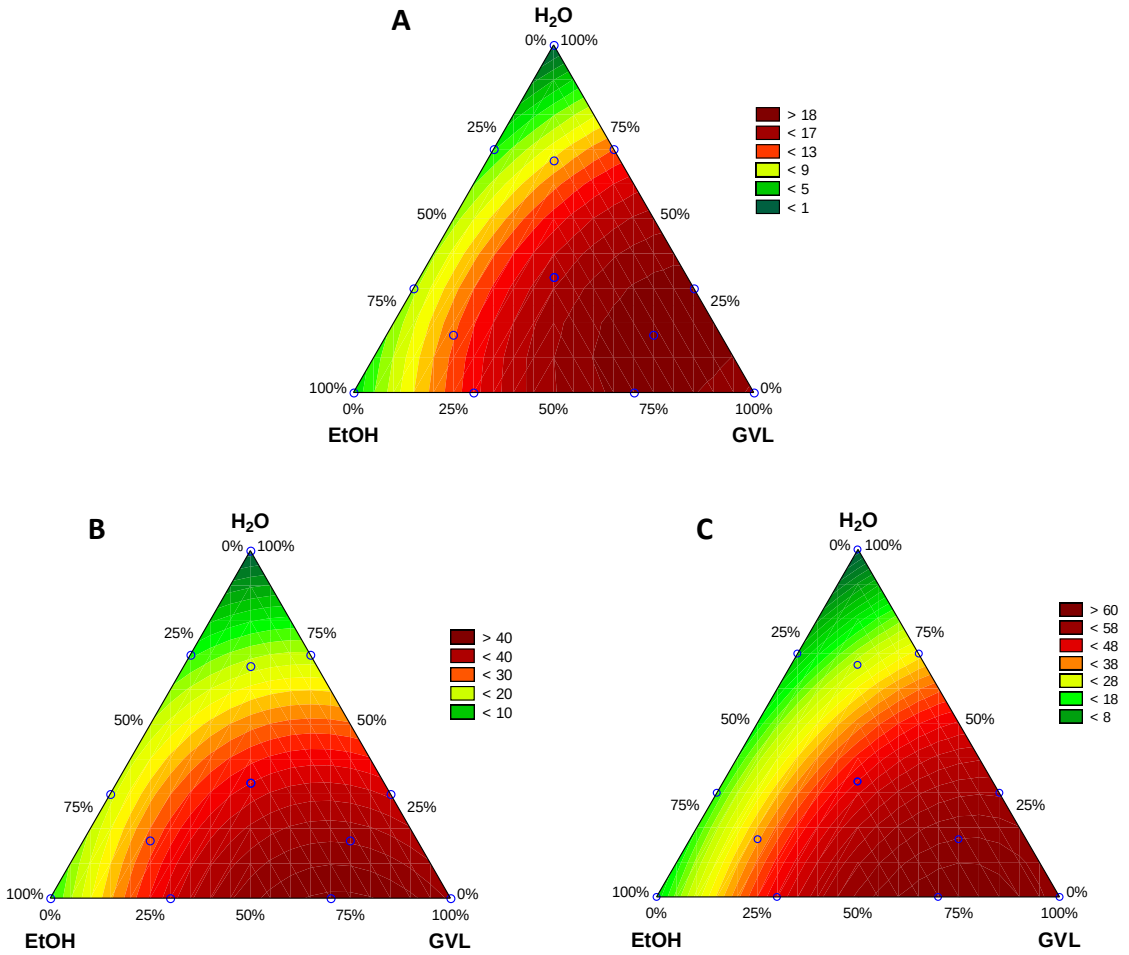

Figure 14. Response surface of (A) TPC (mg GAE/g DW), (B) FRAP (mg TE/g DW) and (C) ABTS (mg TE/g DW), as a function of the composition of the ternary mixture in weight percentage (GVL, EtOH and H_2O). Fixed conditions: solid-liquid ratio of 0.050 and 60 min of extraction time, at 25 °C.

In Figure 14 are represented the ternary diagrams of the influence of solvent composition – ranging from 0 to 100 wt % of GVL, EtOH and H_2O – on phenolic content (TPC) and antioxidant activity (FRAP and ABTS). All experimental data are detailed in Appendix B.2 (Tables B.2.3-B.2.5) The isolated components GVL and EtOH and the interaction between GVL, EtOH and H_2O, had an influence on the studied responses, as can be seen in Pareto Charts (Figures B.2.2, Appendix B.2). According to Figure 14 and Figure B.2.2 (Appendix B.2), GVL was the most significant component, followed by EtOH. In fact, from the bottom side of the triangles presented in Figure 14, it seemed that higher content of GVL, around 70 wt % led to extracts with higher content of phenolic compounds and antioxidant activity. However, mixtures with values above 70 wt % of GVL seemed to decrease the three responses variables under study. It was also possible to observe a significant decrease in the phenolic content and antioxidant activity with the increase of the H_2O fraction in the mixture, especially above 75 wt %, which can be related to the low

solubility hydrophobic compounds in aqueous solutions, as mentioned before. On the other hand, lower weight percentages of H_2O and EtOH affected the response variables positively since it confers a lower viscosity to the final solution, allowing to increase the mass transfer of phenolic compounds to the media [103,104]. Still, as can be seen in the ternary diagrams and in the Pareto chart (Figure B.2.2), EtOH presents a higher effect in the increase of phenolic content and antioxidant activity than H_2O. Therefore, the optimal solvent composition to maximize the phenolic content and antioxidant activity of the extract, considering all responses variables (TPC, FRAP and ABTS), was the mixture composed of GVL:EtOH at the weight ratio of 7:3 (*cf.* Figure B.2.3, Appendix B.2), which allowed to obtain an extract with TPC of (19 ± 1) mg GAE/g DW and antioxidant activity of (47 ± 1) mg TE/g DW by FRAP and (70 ± 2) mg TE/g DW by ABTS.

3.2.4. Optimization of extraction conditions

The univariate analysis for operational conditions optimization ignores the interplay between variables and may not correspond to the overall optimal conditions. A RSM was used to determine the relationship between the independent variables (solid-liquid ratio, extraction time and temperature or amplitude) and the responses (TPC, FRAP and ABTS) and optimize the operating conditions. This methodology evaluates the dependence of the responses (TPC, FRAP and ABTS) to the independent variables that might influence the extraction. In this work, three 2^3 (3 variables and 2 levels) factorial plans were executed. Each factorial planning was carried out using a different extraction technique - a more conventional approach, the CE, and two alternative techniques, the UAE and MAE, aiming to compare their efficiency. All extractions were done by using the biobased solvent mixture previously optimized, GVL:EtOH in the ratio of 7:3 (wt/wt).

The results obtained through the RSM with the combined effects are depicted in Figures 15 to 17. The experimental conditions, the TPC, FRAP and ABTS experimental results and respective calculated values, and the statistical analyzes are provided in Appendix B.2 (Figures B.2.4-B.2.6 and B.2.8-B.2.13, Tables B.2.6-B.2.8 and B.2.10-B.2.15). It was used the variance analysis (ANOVA) to estimate the statistical significance of the variables and the interactions between them. For all response surfaces, and independently of the extraction technique evaluated, the equation of the adjusted polynomial presented a R^2 value above 0.89 and R^2_{adj} higher than 0.79, demonstrating that there were no significant deviations between the experimental and predicted responses, and the established statistical models were suitable.

3.2.4.1. Conventional extraction (CE)

The effect of the three independent variables - solid-liquid ratio, extraction time and temperature - on the phenolic content and antioxidant activity of the extracts were obtained with CE. The results are presented in Figure 15 and in Appendix B.2, Tables B.2.6-B.2.8 and Figures B.2.4-B.2.6.

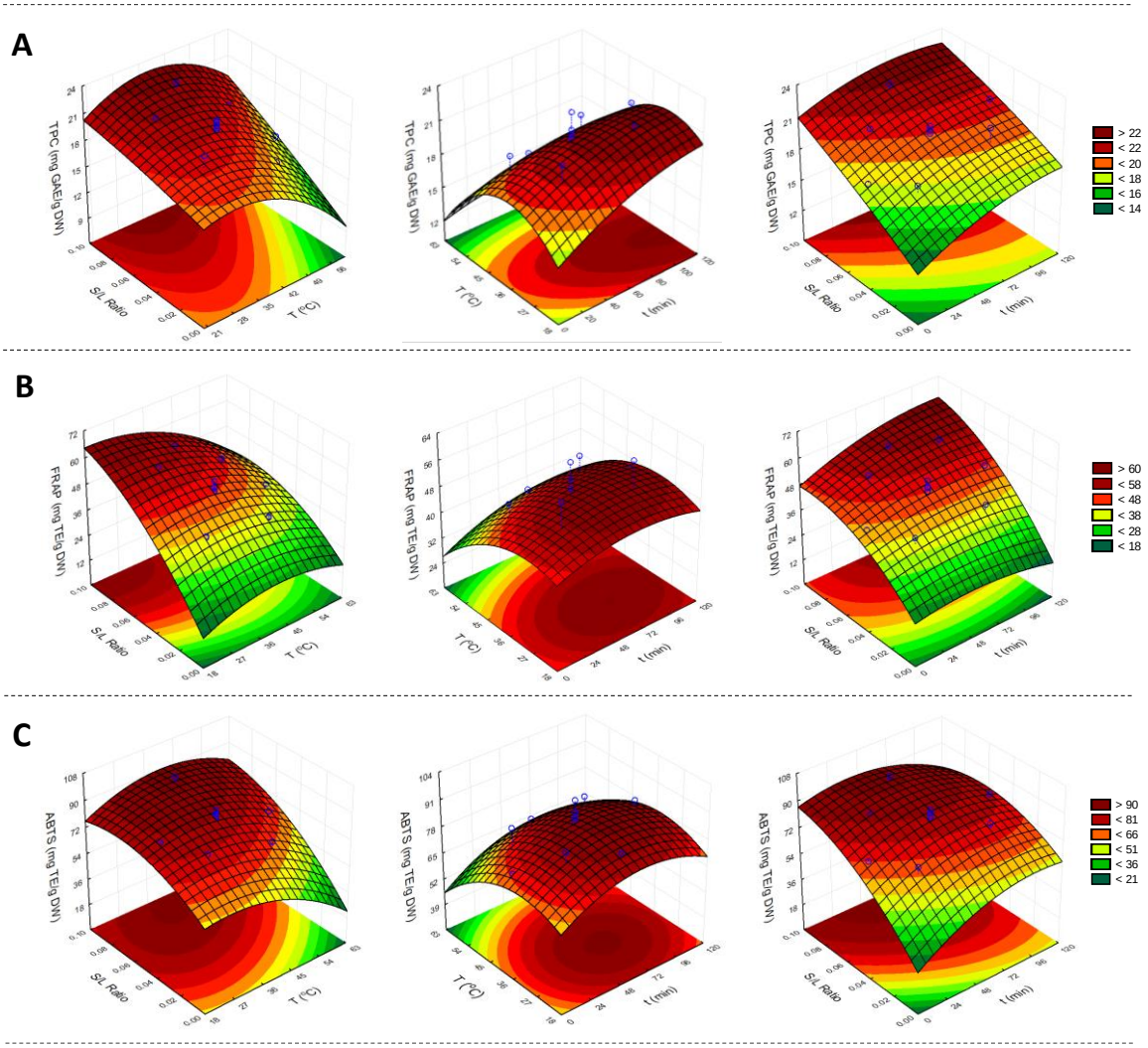

Figure 15. Response surface plot of (A) TPC, (B) FRAP and (C) ABTS assays, representing the influence of solid-liquid ratio and temperature (left side); temperature and time (middle), and solid-liquid ratio and time (right side), for the CE technique using a mixture of GVL:EtOH (7:3, wt/wt).

For the three responses variables in study (TPC, FRAP and ABTS), the solid-liquid ratio was the most significant variable, followed by the temperature and the extraction time, as evidenced in the Pareto chart (Figure B.2.5, Appendix B.2). Solid-liquid ratio and extraction time had a positive effect, *i.e.*, the phenolic content and antioxidant activity increased with the increase of these variables. Temperature had a positive impact on the phenolic content and antioxidant

activity of the obtained extracts until a certain point, leading to maximum values at temperatures between 25 °C and 40 °C.

To obtain an extract with high phenolic content and high antioxidant activity, it is necessary to reach a compromise between the different studied variables to maximize the three responses. Here, the best conditions identified were *T* = 36 °C, S/L ratio = 0.084 and *t* = 60 min (Figure B.2.6, Appendix B.2). Since the optimal solid-liquid ratio was also the maximum value used in the experimental planning, temperature and time optimal conditions were evaluated at higher solid-liquid ratio values (0.100 and 0.120). The results showed that the increase of the solid-liquid ratio above 0.084 had no positive effect on the phenolic content and antioxidant activities of the extracts (*cf.* Figure B.2.7 and Table B.2.9, Appendix B.2). confirming the optimal extractions conditions determined in the experimental planning. At these conditions the following experimental results were: TPC = (21.4 ± 0.5) mg GAE/g DW, FRAP = (61.3 ± 0.4) mg TE/g DW and ABTS = (92.0 ± 0.8) mg TE/g DW (for predicted results, see Table B.2.6-B.2.8). In fact, experimental and predicted results were very similar, which demonstrated the good predictive ability of these models.

3.2.4.2. Utrasound-assisted extraction (UAE)

The effect of the ultrasound extraction technique on the phenolic content and antioxidant activity was evaluated by considering the following variables: solid-liquid ratio, extraction time and amplitude. Here amplitude (%) was used instead of temperature, since this was the variable that ultrasounds equipment allowed to be controlled. Still, the temperature was measured during the extraction procedures, varying in a similar range to that used in CE (30 ^{o}C to 58 ^{o}C). The influence of the three variables on the phenolic content and antioxidant activity when the extractions were performed by UAE is presented in Figure 16, and more details can be found in Appendix B.2 (Tables B.2.10-B.2.12 and Figures B.2.8-B.2.10).

According to Pareto Charts (Figure B.2.9, Appendix B.2) and data depicted in Figure 16, all variables and their interactions were significant for the three responses under evaluation; however the influence level were different. The extraction time had a positive effect in all responses, *i.e*, as longer is the extraction time better was the value of the responses, leading to responses maximum values at extraction times between 10 and 12 min. Furthermore, this variable was the most significant for FRAP and ABTS responses, while presenting a slightly lower impact on TPC. On the other hand, the solid-liquid ratio also increased the phenolic content and antioxidant activity of the extracts up to a certain point, with responses maximum values observed at a solid-liquid ratio between 0.060 and 0.080. In what concerns the amplitude, this

variable also influenced the responses, especially FRAP and ABTS - increasing the amplitude percentage increases the responses values.

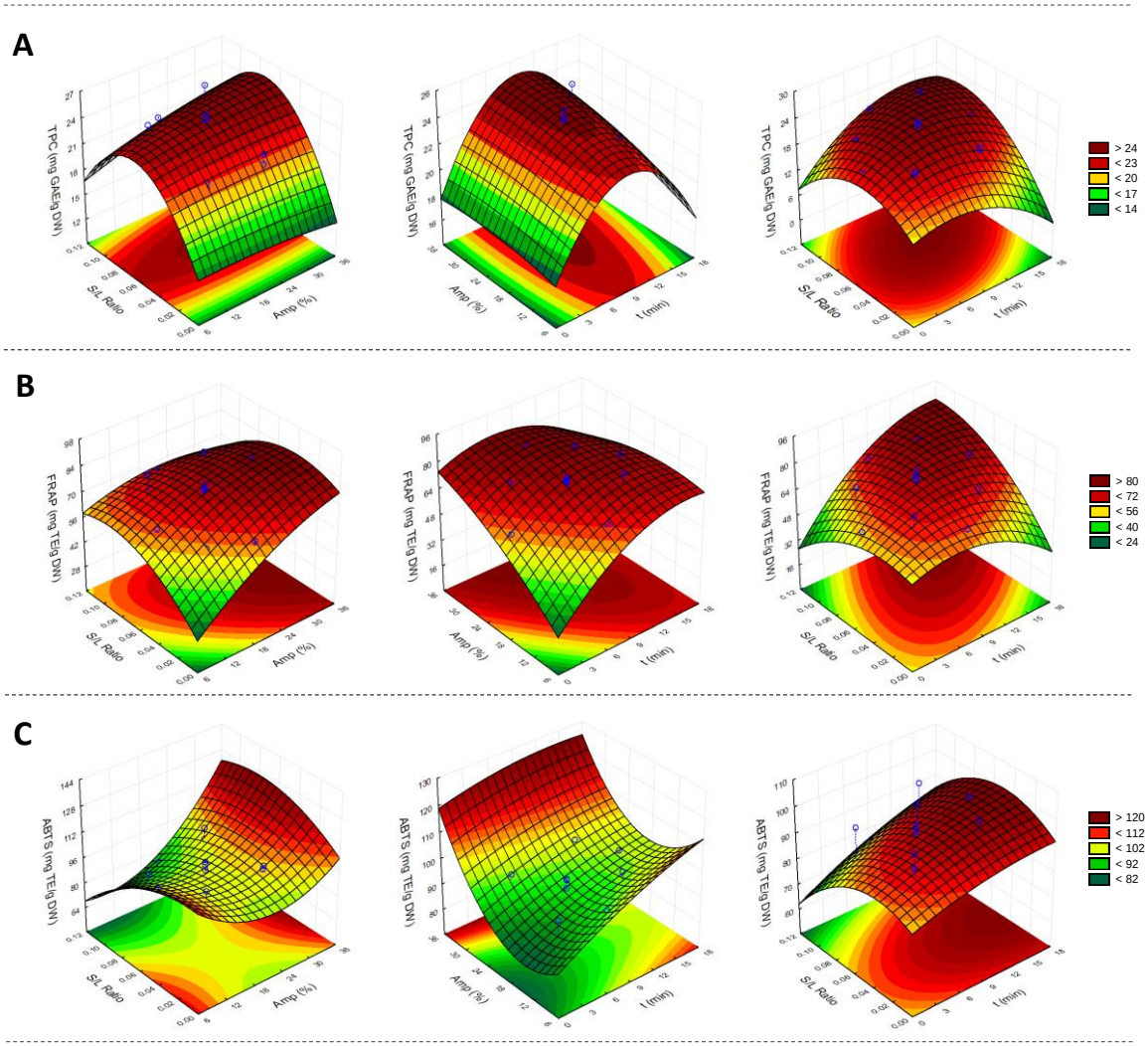

Figure 16. Response surface plots of (A) TPC, (B) FRAP and (C) ABTS assays, representing the influence of solid-liquid ratio and amplitude (left side); amplitude and time (middle), and solid-liquid ratio and time (right side), for the UAE technique, using a mixture of GVL:EtOH (7:3, wt/wt).

Aiming for a good compromise between the different extraction conditions, the following operating conditions for UAE were determined: Amp = 28 %, S/L ratio = 0.077 and *t* = 12 min (*cf.* Figure B.2.10, Appendix B.2). At these conditions, the experimental results were: TPC = (24 ± 1) mg GAE/g DW, FRAP = (81 ± 4) mg TE/g DW and ABTS = (104 ± 2) mg TE/g DW (for predicted results, see Table B.2.10-B.2.12). As previously observed for CE, there was also a good similarly between the experimental and predicted data for UAE, demonstrating the good predictive capacity of the models developed in this work.

3.2.4.3. Microwave-assisted extraction (MAE)

A last factorial planning was carried out for MAE. The variables evaluated were again the temperature, the solid-liquid ratio, and the extraction time. In Figure 17 and Appendix B.2 (Tables B.2.13-B.2.15 and Figures B.2.11-B.2.13) are presented the results obtained concerning the influence of each variable in the phenolic content (TPC) and antioxidant activity (FRAP and ABTS) for the extracts obtained using MAE.

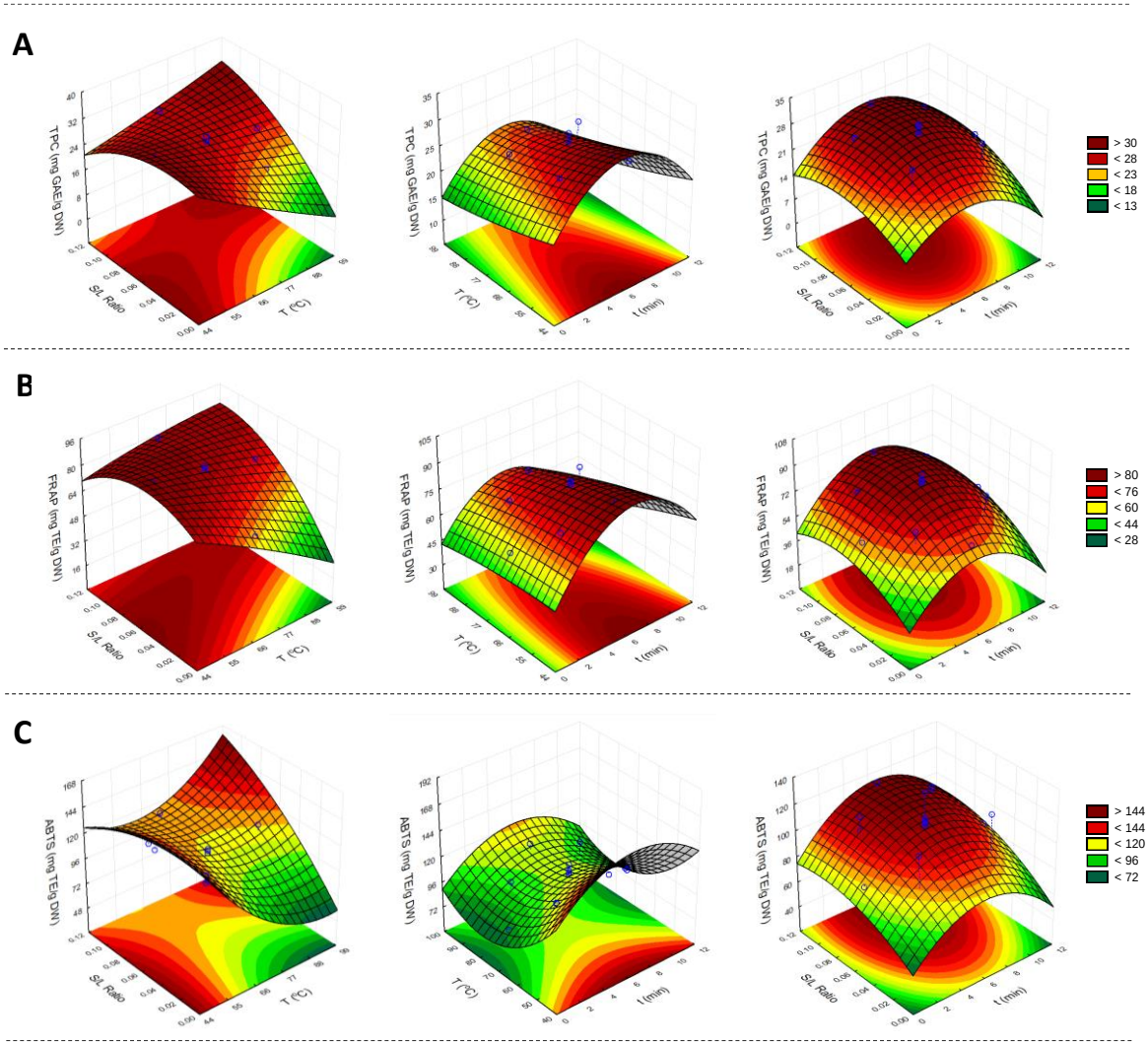

Figure 17. Response surface plots of (A) TPC, (B) FRAP and (C) ABTS assays, representing the influence of solid-liquid ratio and temperature (left side); temperature and time (middle), and solid-liquid ratio and time (right side), for the MAE technique, using a mixture of GVL:EtOH (7:3, wt/wt).

In general, all the variables - extraction time, solid-liquid ratio and temperature - and their interactions were significant variables for the three responses under study, as can be seen in the Pareto Charts (Figure B.2.12, Appendix B.2) and data depicted in Figure 17. The extraction time variable was the most significant for TPC and FRAP, while it was the second most significant for

ABTS (temperature was the most significant). Still, it had a positive effect until cert point in all responses, leading to maximum values at extraction times between 5 and 7 min. In the same line, the solid-liquid ratio also had a positive effect until certain point in all responses, meaning that maximum values were reached at solid-liquid ratios between 0.050 and 0.070. In what concerns the temperature effect, this variable had a negative effect, *i.e.,* the increase of temperature led to a decrease of the response variables, especially on the ABTS, being the best results for phenolic content and antioxidant activity obtained to the lowest temperature evaluated (50 °C). Note that, temperatures below 50 °C were not tested due to microwave equipment limitations.

The optimal conditions determined for MAE were *T* = 50 °C, S/L Ratio = 0.060 and *t* = 6 min (*cf.* Figure B.2.13, Appendix B.2). At the optimal point the following experimental results were: TPC = (29.7 ± 0.6) mg GAE/g DW, FRAP = (87 ± 4) mg TE/g DW and ABTS = (131 ± 1) mg TE/g DW (for predicted results, see Table B.2.13-B.2.15). By the comparison of experimental and predicted values, again, it can be verified the good predictive ability of the models. Furthermore, the results obtained with MAE were very promising, since this extraction technique allowed to obtain the extracts with the highest phenolic content and antioxidant activity determined in this work.

3.2.5. Determination of the main phenolic compounds

The extracts obtained by MAE using the biobased solvent mixture GVL:EtOH (7:3, wt/wt) and the conventional solvents EtOH:H_2O (7:3, wt/wt) and pure Ace, for comparison purposes, at the optimizing extractions conditions were analyzed by UHPLC-UV-MS^n to identify the main phenolic compounds present in the extracts. Among the analysis carried out, it was possible to identify epicatechin, caffeic acid, and quercetin (Figure B.2.14 and Table B.2.16, Appendix B.2), which is in agreement with the results previously reported in other studies regarding the extraction of phenolic compounds from kiwi peels using organic solvents [36,38]. However, these studies were not concluded on time to present all the results in the current thesis. As future work the characterization of the extracts obtained with CE and UAE will be also carried out.

3.2.6. Discussion

UAE and MAE are well-known advanced extraction techniques, of high efficiency and less time consuming. Still, these are also considered expensive techniques due to their high energy consumption. In contrast to these sophisticated approaches, traditional extraction with temperature and stirring control is the cheapest to set up, but presents variable efficiency and

is time-consuming. To assess the efficiency of different techniques evaluated in this work - CE, UAE and MAE - in the extraction of phenolic compounds from kiwi peels, two analyses were done. First, the extracts obtained at optimal conditions were compared in terms of phenolic content (TPC) and antioxidant activity (FRAP and ABTS) - Table 9. Extracts obtained by using the most efficient biobased solvent mixture - GVL:EtOH (7:3, wt/wt) – and conventional solvents – EtOH: H_2O (7:3, wt/wt) and pure Ace – for comparison purposes. Second, a study considering the energy costs of each technique and its efficiency in phenolic compounds extraction was done to understand the advantages and disadvantages of each, to choose the extraction technique that best suits the aim of this work.

From the results presented in Table 9, when Ace and the biobased solvent mixture were used, it is possible to obtain extracts richer in phenolic compounds and with higher antioxidant activity in the following order of extraction technique: MAE > UAE > CE. For the EtOH/H_2O mixture, the UAE allowed to obtain better results than MAE. Thus, the alternative techniques (UAE and MAE) showed to be viable alternatives to the CE to obtain an extract with the desired composition in a short extraction time. The MAE appeared as one of the most promising techniques evaluated here, since it allowed to obtain extracts with the higher phenolic content and higher antioxidant activity in a shorter extraction time (10x and 2x less than CE and UAE, respectively) and by using a slightly lower solid-liquid ratio when compared with other two techniques. Concerning the comparison between solvents efficiency at the optimal conditions of extraction, these showed the following trend when considering TPC, FRAP and ABTS results: GVL:EtOH (7:3, wt/wt) > Ace > EtOH:H_2O (7:3, wt/wt). This trend is independent of the extraction technique used. These results highlight the potential of biobased solvents mixtures to be used to extract phenolic compounds with high antioxidant activity from biomass and their potential as substitutes of more conventional solvents. Furthermore, the obtained extracts might be used directly as a final product after the extraction process since GVL and EtOH are compounds authorized as food additives [91,135].

Table 9. Phenolic content and antioxidant activity of the extracts obtained using GVL:EtOH (7:3, wt/wt), Ace and EtOH: H_2O (7:3,wt/wt) at the optimized extraction conditions with CE, UAE and MAE.

		Variables				TPC (mg GAE/g DW)	FRAP (mg TE/g DW)	ABTS (mg TE/g DW)
		Amp (%)	*t* (min)	S/L Ratio	*T* (°C)			
GVL:EtOH (7:3, wt/wt)	**CE**	---	60.0	0.084	36	21.4 $^{C, c}$ ± 0.5	61.3 ^{B,c} ± 0.4	92.0 ^{C,d} ± 0.8
	UAE	28	11.7	0.077	~51	24 $^{B, b}$ ± 1	81 ^{A,b} ± 4	104 ^{B,c} ± 2
	MAE	---	6.0	0.060	50	29.7 $^{A, a}$ ± 0.6	87 ^{A,a} ± 4	131 ^{A,a} ± 1
Ace (pure)	**CE**	---	60.0	0.084	36	19.3 $^{B, d}$ ± 0.8	59.7 ^{C,c} ± 0.8	83 ^{C,e} ± 2
	UAE	28	11.7	0.077	~51	24 $^{A, b}$ ± 2	78.4 ^{B,b} ± 0.9	95 ^{B,d} ± 1
	MAE	---	6.0	0.060	50	24.8 $^{A, b}$ ± 0.4	85.0 ^{A,a} ± 0.8	119 ^{A,b} ± 5
EtOH: H_2O (7:3, wt/wt)	**CE**	---	60.0	0.084	36	12 $^{C, f,}$ ± 1	37 ^{C,e} ± 1	52 ^{C,g} ± 2
	UAE	28	11.7	0.077	~51	19.7 $^{A, d}$ ± 0.4	58 ^{B,c} ± 3	82 ^{A,e} ± 4
	MAE	---	6.0	0.060	50	17 $^{A, e}$ ± 1	49 ^{A,d} ± 2	69 ^{B,f} ± 2

Results expressed as mean ± standard deviation. Different letters in the same column represent significant difference according to Fisher's LSD test ($p < 0.05$). Capital letters: significance of extraction techniques for each solvent in study. Lowercase letters: Significance of all extraction techniques and solvents in study.

Finally, the equation 6 suggested by Passos *et al.* [105] was used to evaluate in a simple way the economic viability of the extraction techniques (CE, UAE, and MAE) proposed here. This equation 6 [105] is a simplified model that relates the return (R) associated with the extraction of a particular value-added compound when alternative solvents, in this case, biobased solvents (BB) are used as extraction solvents, and which suffer a slight modification to account with the energetic costs (γ), as showed below:

$$R = [C_{\mathrm{pro}} \times €_{prod} - €_{biom}] - [V_{\mathrm{BB}} \times €_{BB} \times r_{BB\ lost} \times \alpha + \beta] - \gamma \qquad \text{(Equation 6)}$$

The variable C_{prod} is the concentration of the target compounds in the biomass (here TPC results were considered), $€_{\mathrm{prod}}$ is the price of the product per kg, and $€_{\mathrm{biom}}$ is the cost associated with the biomass (which here was considered zero since the biomass used is a by-product). The extraction process cost is assumed to be proportional to the cost of BB lost per each kg of biomass treated. The variable V_{BB} is the volume of the BB needed to treat one kg of biomass, $€_{\mathrm{BB}}$ is the price per kg, and $r_{\mathrm{BB\ lost}}$ is the ratio of BB lost during the recycling approach, which is 1 since in this study is not pretended to recycle the BB. The factor α and β represent the proportional costs of the process and nonproportional costs, respectively. With the application of this equation, it is possible to know which variables exhibit a significant impact on the return of a given process.

Despite MAE leads to an improved extraction yield in relation to UAE and CE techniques for phenolic compounds and antioxidant activity of the kiwi peels extracts, this technique has a high energy consumption compared to the other techniques, especially in relation to CE (Table 10), being thus important to consider the energy costs of the process. Moreover, it is also important to consider that recycling the biobased solvent is not proposed in the extraction process; instead, it is suggested to be present in the final formulation. Thus, in our case, the energy consumption related to each technique and the cost of the biobased solvent (GVL) are the main factors in the final product cost. Looking for our process, CE, UAE and MAE processes used a solid-liquid ratio of 0.084, 0.077 and 0.060, respectively, and a BB concentration of GVL:EtOH (7:3 wt/wt), the price of BB will be 3.73 €/L, considering that industrial reagents are acquired [136] and without the recovery of the BB ($r_{\mathrm{BB\ lost}}$ = 1). Moreover, the energetic inputs used are presented in Table 10, and it was considered that 1 kWh costs 0.14 €. In Figure 18 is possible to see a linear relationship between the return and the production cost for all techniques if a negligible cost of the biomass is assumed ($€_{\mathrm{biom}}$ = 0). The results showed that UAE is preferable to the CE in all scenarios. Furthermore, and as expected, the high energy consumption of MAE has a significant impact and this technique is only preferable when the cost of the product is

higher than 115 €/g and 182 €/g in relation to CE and UAE, respectively (Figure 18). In summary, MAE technique is a good option when very expensive phenolic compounds are extracted, but, for the cheaper ones the UAE technique is preferable, with the CE being not recommended for any scenario. Since our extract is reach in epicatechin and its derivates, and their price at Sigma Aldrich is 126 €/g [137], the UAE is the preferable extraction technique in this case.

Table 10. Consumed energy expressed by joules (J) in each optimal extraction conditions from CE, UAE and MAE.

	Amp (%)	T (min)	S/L Ratio	T (ºC)	Consumed energy (J)
CE	---	60	0.084	36	32700
UAE	28	12	0.077	~51	43920
MAE	---	6	0.06	50	45480

*It was considered the price of light for a homecase.

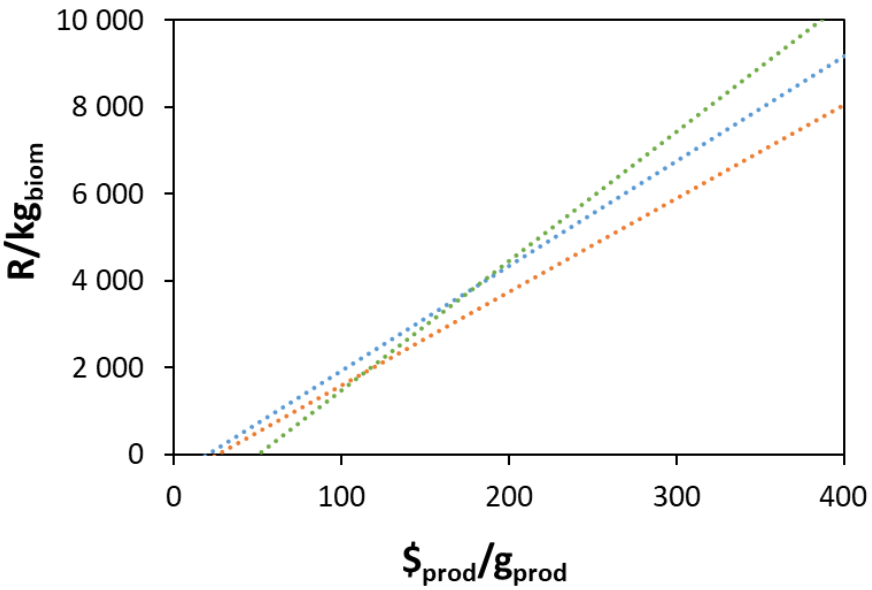

Figure 18. Return obtained for each kg of treated biomass as a function of the phenolic compounds cost for each technique – CE (orange), UAE (blue), MAE (green).

3.2.7. Conclusions

In this work, for the first time, alternative extraction techniques were combined with alternative biobased solvents and their mixtures to replace frequently used volatile organic solvents for the extraction of phenolic compounds from kiwi. A preliminary study identified kiwi peels as the most promising kiwi residue to obtain an extract rich in phenolic compounds. A screening of biobased solvents mixtures with EtOH and/or H_2O revealed that GVL mixtures were the most efficient to obtain extracts with high levels of phenolic compounds and antioxidant activity. Afterwards, by an experimental design, the optimal solvent composition was determined to be GVL:EtOH (7:3, wt/wt). To select the best extraction technique, the extraction conditions (temperature/amplitude, extraction time and solid-liquid ratio) for each extraction technique (CE, UAE and MAE) were optimized by RSM and by using the most efficient biobased solvent mixture. Among the three extraction techniques evaluated, MAE presented the best results, allowing to obtain an extract with the highest content of phenolic compounds and antioxidant activity, requiring short extraction times. Moreover, the biobased solvent mixture GVL:EtOH (7:3 wt/wt) demonstrated higher efficiency compared to conventional solvents for any extraction technique, highlighting the advantages of biobased solvents. Finally, the extracts obtained at the optimizing conditions were analyzed, presenting high levels of epicatechin, quercetin and caffeic acid derivates. Furthermore, some estimated costs of the three extractions processes were provided, demonstrating that the UAE is the extraction technique that is preferable in this process. Thus, this work showed that both alternative techniques and biobased solvents were great tools of green chemistry to extract phenolic compounds from kiwi peels. Furthermore, GVL is here used for the first time as a biomass solvent extraction. The extraction of phenolic compounds from different industrial by-products, such as kiwi peels, using food-grade solvents, such as GVL, has much more potential to better develop industries in order to prepare extracts with a high amount of natural antioxidants, replacing the synthetic antioxidants substances.

4. Final remarks

4.1. Conclusions

This work demonstrated the hydrotropic potential of biobased solvents in the solubility of phenolic compounds and their applicability in the extraction of these compounds from kiwi peels. First, the ability of aqueous solutions of biobased solvents in enhancing the solubility of the phenolic compounds usually present in kiwi, such as ferulic acid, syringic acid and catechin, was evaluated. The results obtained showed that aqueous solutions of GVL lead to higher increments on the solubility of the phenolic compounds, up to 61-fold, 99-fold and 237-fold for catechin, syringic acid and ferulic acid, respectively, when compared to pure water. Through the Setschenow constant, it was possible to demonstrate that the hydrotropy mechanism depends on both the hydrotrope and the solute. It was shown that hydrotropes hydrophobicity plays an important role in the solubility enhancement at hydrotrope diluted region. The cooperative hydrotropy model was applied to fit the experimental data and it was identified a relation between the parameter *m* and the hydrotrope log(K_{OW}). By comparing the different hydrotrope concentration regions it was concluded that hydrotropes of higher hydrophobicity have a higher tendency for aggregation at higher concentrations resulting in a lower solute solubility enhancement. Solute hydrophobicity correlates well with the maximum solubility enhancement obtained, while seems to have no effect at hydrotrope lower concentrations.

Confirmed the potential of biobased solvents to increase the solubility of phenolic compounds, the next step addressed the actual application of biobased solvent mixtures to extract phenolic compounds from kiwi peels. The use of biobased solvents was combined with alternative techniques, aiming for a better extraction efficiency when compared with traditional solvents and techniques. In general, mixtures of biobased solvents in ethanol and/or water showed a higher phenolic content and antioxidant activity than conventional solvents, with mixtures of GVL attaining the best results. The composition of GVL mixtures was optimized to GVL:EtOH (7:3, wt/wt). The RSM carried out to optimize the operational conditions for each technique (CE, UAE and MAE) showed that MAE is the technique that leads to the extract with the higher content of phenolics and antioxidant activity, in the shortest extraction time. Furthermore, the optimized biobased solvent (GVL:ethanol in a ratio of 7:3, wt/wt) evidences a better efficiency than conventional solvents, in all techniques, demonstrating the power of biobased solvents in the extraction process. Moreover, the extracts are mainly composed by epicatechin, caffeic acid and quercetin. Finally, an economic study was developed to evaluate the most promissory extraction technique (CE, UAE and MAE), and was showed that UAE is the desirable technique.

In summary, it is here demonstrated the ability of biobased solvents to increase the solubility of phenolic compounds in water. These solvents also appeared as promising to replace volatile organic solvents used in the extraction of phenolic compounds from kiwi waste. Additionally, the combination with alternative extraction techniques increases the efficiency of extraction yield, resulting in higher phenolic content and higher antioxidant activity than those obtained with CE. Thus, the results obtained prove that biobased solvents combined with alternative extraction techniques can lead to the effective extraction of phenolic compounds from kiwi peels, working as a base for the development of more sustainable and efficient extraction processes to recover natural products from food industry wastes, contributing to the valorization of natural resources.

4.2. Future work

As future work, it will be interesting to perform solubility tests with a broader range of bio-based solvents and phenolic compounds, to better understand the mechanism ruling the phenomenon of hydrotropy. Concerning the extraction techniques, it is important to characterize also the extracts obtained by using the CE and UAE techniques, and quantify the compounds identified, confirming if there is a compound that stands out. Moreover, the recovery and reuse of the solvents (EtOH and GVL) should be studied, as well as if the extract's phenolic content and antioxidant activity are maintained after the solvent recovery step. If the direct application of the extract on industrial products, namely food industry products, is considered, then it is crucial to carried out cytotoxicity tests and verify the economic viability of this strategy. Finally, it would be very interesting to explore the extraction of phenolic compounds using other alternative techniques, such as high-pressure extraction, to compare the efficiency of this technique with the ones tested in this work.

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6. Scientific Contribution

Conferences

- Sandra S. Silva, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, “Extraction of phenolic compounds from Kiwi waste using biobased solvents”, Jornadas CICECO, Advancing Science Shaping Society, Aveiro, Portugal, October 2021. (Online)
- Sandra S. Silva, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, "Kiwi waste as a source of value-added compounds: Extraction of phenolic compounds using aqueous solutions of biobased solvents", 19th International Symposium on Solubility Phenomena and Related Equilibrium Processes (ISSP-19), Taipei, Taiwan, July 2021. (Online)
- Sandra S. Silva, Diego Ferro, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, "From Kiwi waste to value-added compounds using aqueous solutions of alternative solvents", 25th Annual Green Chemistry & Engineering Conference (ACS), Reston, USA, June 2021. (Online)
- Sandra S. Silva, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, "Recovery of phenolic compounds from Kiwi waste with aqueous solutions of biobased solvents", 14th Meeting of Physical Chemistry (ENQF), Coimbra, Portugal, March 2021. (Online)

Oral Communication

- Sandra S. Silva, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, “Enhanced extraction of phenolic compounds from Kiwi waste using biobased solvents”: PATh Spring Workshop, Aveiro, Portugal, September 2021.

Awards

- Student Best Poster Awards at 19th International Symposium on Solubility Phenomena and Related Equilibrium Processes, Online, by International Union of Pure and Applied Chemistry (IUPAC), "Kiwi waste as a source of value-added compounds: Extraction of phenolic compounds using aqueous solutions of biobased solvents", July 2021.

Publications

- Sandra S. Silva, Marina Justi, Daniel P. Ribeiro, Jean-Baptiste Chagnoleau, Sónia A. O. Santos, Helena Passos, Ana M. Ferreira and João A.P. Coutinho, “Using biobased solvents for the extraction of phenolic compounds from kiwifruit industry waste" (in preparation).

- Sandra S. Silva, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, “Solubility enhancement of phenolic compounds using aqueous solutions of biobased solvents as hydrotropes" (in preparation).
- Sandra S. Silva, Helena Passos, Ana M. Ferreira, João A.P. Coutinho, “Kiwi (Actinidia deliciosa 'Hayward' byproducts: A potential source for phenolic compounds", (in preparation).

Supervision Experience

- Final project in Biotechnology: Marina Setubal Justi, “Valorization of kiwi residues through the extraction of phenolic compounds”. (Experimental supervision)
- Final project in Biochemistry: Daniel Prazeres Ribeiro, “Extraction of bioactive compounds from kiwi waste with health benefits”. (Experimental supervision)

Appendix A – Experimental procedure

A.1. Solubility data of phenolic compounds

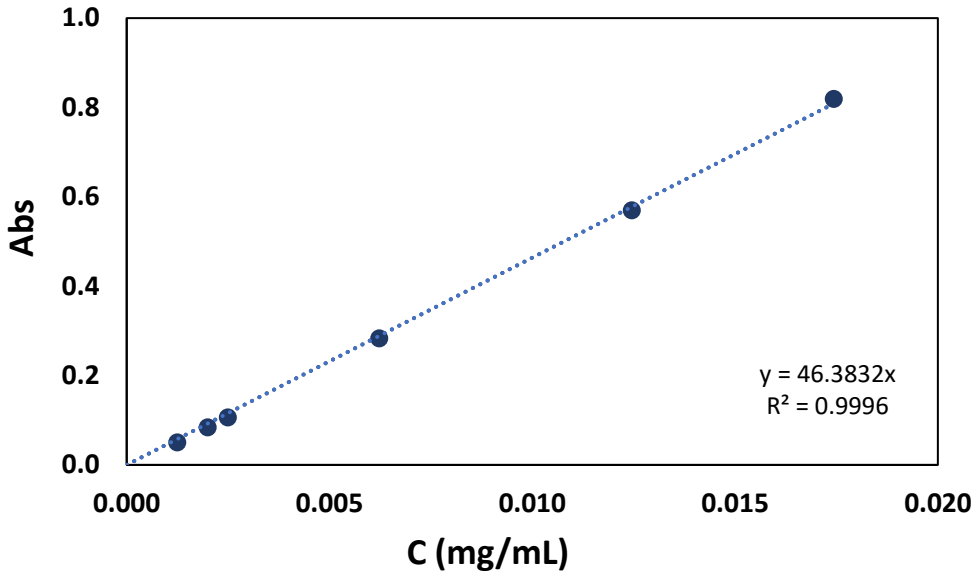

Figure A.1 1. Calibration curve of ferulic acid.

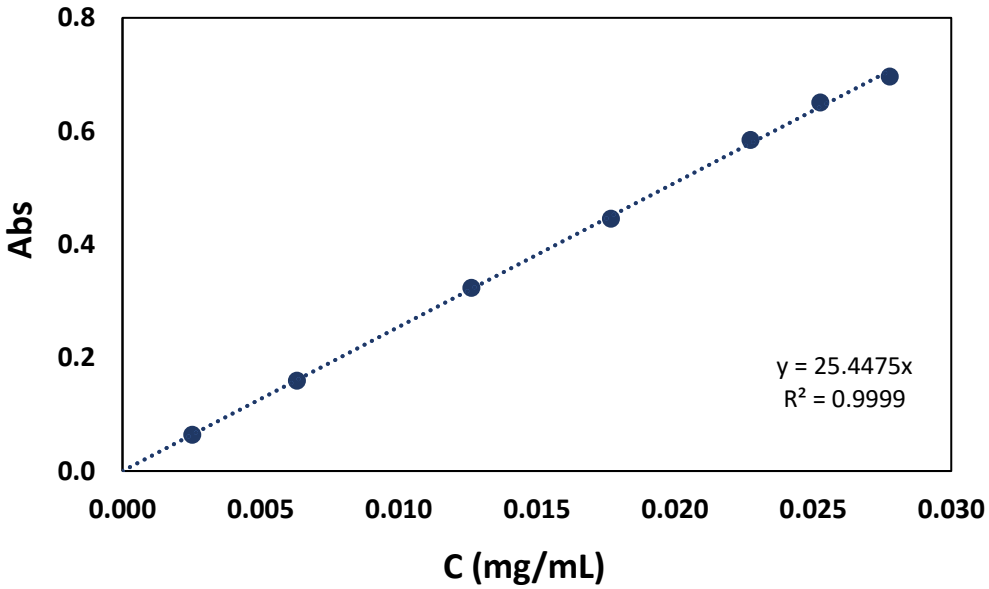

Figure A.1.2. Calibration curve of syringic acid.

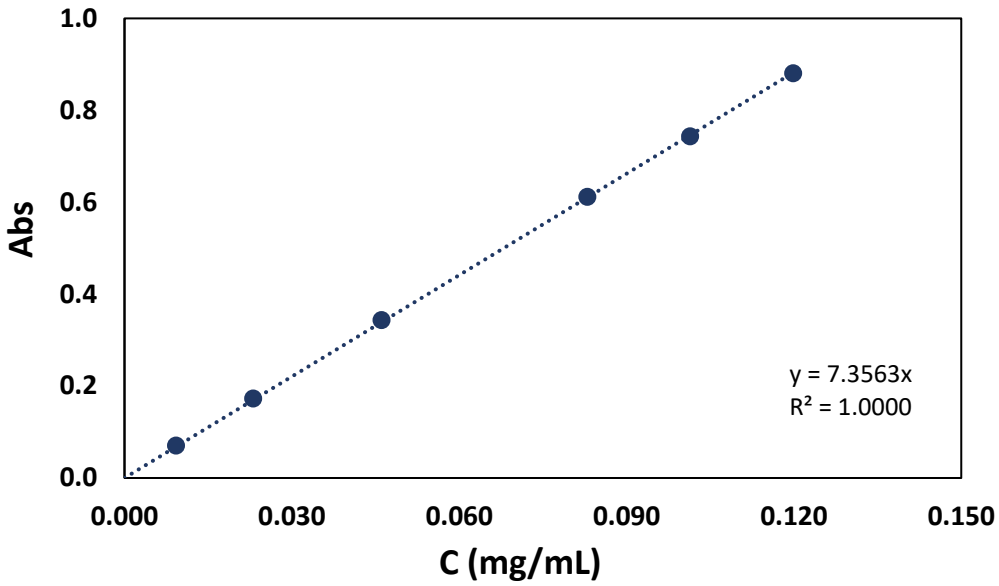

Figure A.1.3. Calibration curve of catechin.

A.2. Extraction of phenolic compounds from kiwi waste

Selection of biomass

Table A.2.1. Phenolic content (TPC) and antioxidant activity (FRAP and ABTS) levels of the extracts obtained using different kiwi parts (peel, pulp, juice and whole fruit) by soxhlet extraction with ethanol.

	Juice	Peel	Pulp	Whole Kiwi
TPC (mg GAE/g DW)	7 ± 1	8.3 ± 0.2	2.05 ± 0.01	7 ± 1
FRAP (mg TE/g DW)	10.4 ± 0.3	16.7 ± 0.5	5 ± 1	11.1 ± 0.4
ABTS (mg TE/g DW)	7.1 ± 0.1	19.9 ± 0.3	3.6 ± 0.1	10.8 ± 0.4

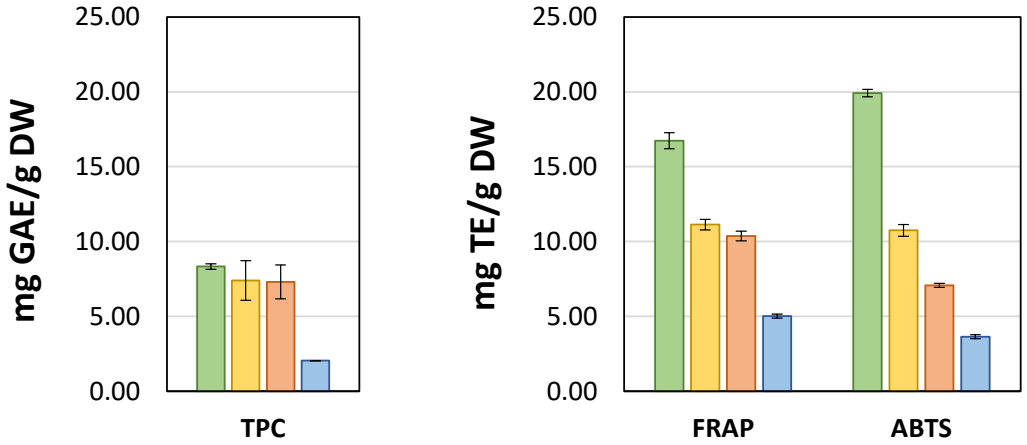

Figure A.2.1. Phenolic content (TPC) and antioxidant activity (FRAP and ABTS) of all kiwi parts: peel (green), whole kiwi (yellow), juice (red) and pulp (blue) obtained by soxhlet extraction.

Selection of storage

Table A.2.2. Phenolic content (TPC) and antioxidant activity (FRAP and ABTS) values from extracts from kiwifruit peels storage at different conditions, using EtOH: H_2O (7:3, wt/wt) in CE.

	biomass dry and stored at -10 °C	biomass directly stored at -10 °C	biomass directly stored at -80 °C
TPC (mg GAE/g DW)	0.8 ± 0.3	3.33 ± 0.06	8.8 ± 0.8
FRAP (mg TE/g DW)	1.3 ± 0.1	20 ± 2	24 ± 1
ABTS (mg TE/g DW)	1.6 ± 0.2	19.8 ± 0.6	25.0 ± 0.6

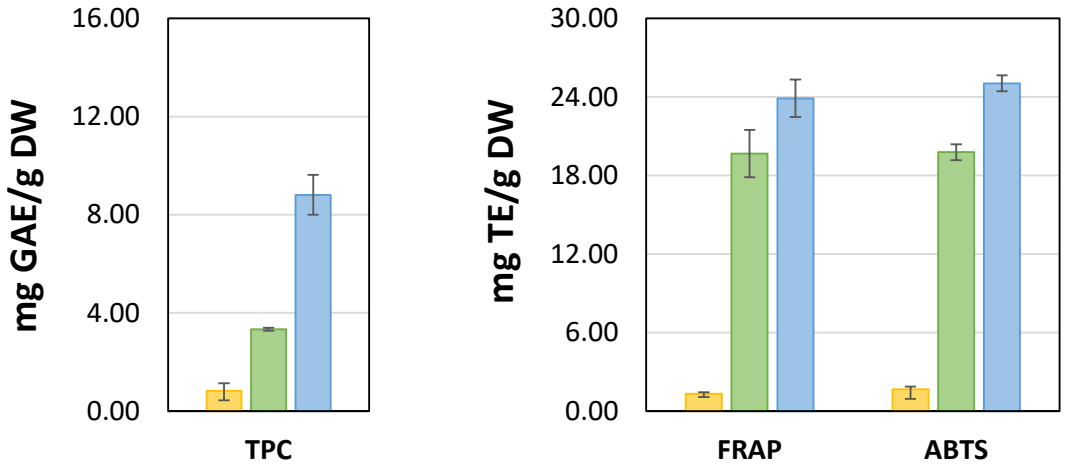

Figure A.2.2. Phenolic content (TPC) and antioxidant activity (FRAP and ABTS) values of different forms of storage: biomass dry and stored at -10 ºC (yellow), biomass directly stored at -10 ºC (green) and biomass directly stored at -80 ºC (blue), using EtOH: H_2O (7:3, wt/wt) in CE.

Mixture design

Table A.2.3. Mixture design for optimization of the solvent composition.

Run	Coded variables		
	X_1	X_2	X_3
1	0.00	0.67	0.33
2	0.00	0.00	1.00
3	0.33	0.33	0.33
4	0.00	1.00	0.00
5	0.17	0.67	0.17
6	1.00	0.00	0.00
7	0.33	0.67	0.00
8	0.67	0.00	0.33
9	0.00	0.33	0.67
10	0.33	0.33	0.33
11	0.67	0.33	0.00
12	0.17	0.17	0.67
13	0.67	0.17	0.17
14	0.33	0.00	0.67

Factorial planning

Table A.2.4. Factorial planning (2^3) for the optimization of operating conditions by response surface methodology (RSM).

Run	Coded variables		
	X_1	X_2	X_3
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1
9	-1.68	0	0
10	1.68	0	0
11	0	-1.68	0
12	0	1.68	0
13	0	0	-1.68
14	0	0	1.68
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0

Table A.2.5. Coded levels of independents variables used in the factorial planning for the optimization of operating conditions by conventional extraction (CE).

Independent variables	Axial	Factorial	Central	Factorial	Axial
	-1.682	**-1**	**0**	**1**	**1.68**
Temperature (°C) -X1	23	30	40	50	57
Time (min) - X2	9.5	30.0	60.0	90.0	110.4
Solid-liquid ratio - X3	0.016	0.030	0.050	0.070	0.084

Table A.2.6. Coded levels of independents variables used in the factorial planning for the optimization of operating conditions by ultrasound-assisted extraction (UAE).

Independent variables	Axial	Factorial	Central	Factorial	Axial
	-1.682	**-1**	**0**	**1**	**1.68**
Amplitude (%) - X1	10	14	20	26	30
Time (min) - X2	1.3	4.0	8.0	12.0	14.7
Solid-liquid ratio - X3	0.010	0.030	0.060	0.090	0.110

Table A.2.7. Coded levels of independents variables used in the factorial planning for the optimization of operating conditions by microwave-assisted extraction (MAE).

Independent variables	Axial	Factorial	Central	Factorial	Axial
	-1.682	**-1**	**0**	**1**	**1.68**
Temperature (°C) - X1	50	58	70	82	90
Time (min) - X2	1.0	3.0	6.0	9.0	11.0
Solid-liquid ratio - X3	0.010	0.030	0.060	0.090	0.110

Appendix B - Results and Discussion

B.1. Solubility data of phenolic compounds

Hydrotopy data

Table B.1.1. Solubility enhancement (S/S_0) of ferulic acid in aqueous solutions of biobased solvents.

wt %	CYR	GVL	HEX	PRO
0.00	1.00 ± 0.06	1.00 ± 0.06	1.00 ± 0.06	1.00 ± 0.06
1.00	1.12 ± 0.09	1.27 ± 0.08	1.3 ± 0.2	1.11 ± 0.01
2.00	1.27 ± 0.07	1.47 ± 0.09	1.38 ± 0.01	1.23 ± 0.06
3.00	1.43 ± 0.01	1.72 ± 0.06	1.8 ± 0.1	1.4 ± 0.2
4.00	1.6 ± 0.2	2.01 ± 0.03	2.0 ± 0.1	1.40 ± 0.03
5.00	1.76 ± 0.04	2.5 ± 0.1	2.5 ± 0.2	1.65 ± 0.05
12.00	2.2 ± 0.3	5.01 ± 0.05	4.87 ± 0.09	1.7 ± 0.1
20.00	3.6 ± 0.1	23 ± 2	18.0 ± 0.3	2.9 ± 0.2
30.00	6.3 ± 0.7	55 ± 2	36.8 ± 0.6	5.1 ± 0.3
40.00	14.1 ± 0.8	101.1 ± 0.5	71 ± 3	9.4 ± 0.3
50.00	34 ± 1	159 ± 2	92 ± 1	18.0 ± 0.5
60.00	75 ± 6	196.4 ± 0.3	110 ± 3	32 ± 1
70.00	112 ± 5	231 ± 2	124 ± 4	46.9 ± 0.6
80.00	139 ± 3	237 ± 2	130 ± 3	67 ± 1
90.00	147 ± 7	229 ± 3	133 ± 3	84 ± 1
92.00	143 ± 2	228 ± 3	---	85.9 ± 0.5
94.00	135 ± 2	218 ± 9	---	89 ± 1
96.00	119 ± 1	193 ± 6	---	91.1 ± 0.4
98.00	89 ± 2	168.5 ± 0.7	---	93.8 ± 0.6
100.00	60 ± 2	133 ± 3	---	97 ± 1

Table B.1.2. Solubility enhancement (S/S_0) of syringic acid in aqueous solutions of biobased solvents.

wt %	CYR	GVL	HEX	PRO
0.00	1.00 ± 0.02	1.00 ± 0.02	1.00 ± 0.02	1.00 ± 0.02
1.00	1.16 ± 0.04	1.2 ± 0.1	1.16 ± 0.05	1.07 ± 0.04
2.00	1.21 ± 0.03	1.4 ± 0.1	1.39 ± 0.06	1.15 ± 0.02
3.00	1.27 ± 0.03	1.6 ± 0.2	1.7 ± 0.1	1.21 ± 0.02
4.00	1.33 ± 0.03	1.9 ± 0.2	2.24 ± 0.06	1.25 ± 0.03
5.00	1.42 ± 0.04	2.0 ± 0.1	2.44 ± 0.05	1.33 ± 0.06
12.00	2.39 ± 0.03	3.9 ± 0.3	4.68 ± 0.04	1.56 ± 0.01
20.00	4.3 ± 0.1	12.0 ± 0.4	12.25 ± 0.08	2.47 ± 0.02
30.00	7.84 ± 0.04	28 ± 1	22.74 ± 0.38	4.17 ± 0.02
40.00	14.97 ± 0.05	44 ± 4	33.6 ± 0.2	7.15 ± 0.04
50.00	23.6 ± 0.1	60.2 ± 0.4	44.2 ± 0.2	11.26 ± 0.01
60.00	40.3 ± 0.7	72.5 ± 0.7	51.9 ± 0.6	18.0 ± 0.3
70.00	51.5 ± 0.9	90.7 ± 0.2	58 ± 1	23.9 ± 0.5
80.00	53 ± 1	98.7 ± 0.3	54.2 ± 0.2	27.4 ± 0.3
90.00	52 ± 3	85.6 ± 0.3	44.6 ± 0.1	31 ± 1
92.00	48.2 ± 0.2	79 ± 1	---	30.0 ± 0.5
94.00	44.2 ± 0.8	71 ± 1	---	30.1 ± 0.4
96.00	36.7 ± 0.4	61.9 ± 0.9	---	30.0 ± 0.3
98.00	26.5 ± 0.6	49.2 ± 0.4	---	30.2 ± 0.5
100.00	14.7 ± 0.2	31.9 ± 0.4	---	29.1 ± 0.6

Table B.1.3. Solubility enhancement (S/S_0) of catechin in aqueous solutions of biobased solvents.

wt %	CYR	GVL	HEX	PRO
0.00	1.00 ± 0.04	1.00 ± 0.04	1.00 ± 0.04	1.00 ± 0.04
1.00	0.07 ± 0.01	1.18 ± 0.09	1.55 ± 0.08	1.23 ± 0.06
2.00	0.08 ± 0.02	1.45 ± 0.05	1.94 ± 0.08	1.4 ± 0.2
3.00	0.10 ± 0.01	1.92 ± 0.05	2.41 ± 0.07	1.69 ± 0.09
4.00	0.11 ± 0.01	2.3 ± 0.1	2.83 ± 0.01	1.8 ± 0.1
5.00	0.14 ± 0.03	2.9 ± 0.2	3.5 ± 0.1	2.04 ± 0.07
12.00	0.21 ± 0.01	7.8 ± 0.3	7.3 ± 0.1	2.8 ± 0.4
20.00	0.67 ± 0.04	18.3 ± 0.6	14.9 ± 0.5	6.8 ± 0.2
30.00	2.4 ± 0.3	27 ± 2	20.6 ± 0.5	13.6 ± 0.1
40.00	4.9 ± 0.6	35.2 ± 0.7	27 ± 3	21 ± 1
50.00	5.8 ± 0.1	45.2 ± 0.5	33.6 ± 0.6	26.4 ± 0.8
60.00	5.8 ± 0.1	52.6 ± 0.4	36.97 ± 0.01	30.5 ± 0.3
70.00	4.9 ± 0.5	57.4 ± 0.5	34.61 ± 0.06	34 ± 2
80.00	4.2 ± 0.5	61.1 ± 0.4	31 ± 1	34 ± 2
90.00	3.9 ± 0.5	62 ± 1	28.16 ± 0.09	33 ± 2
92.00	---	59.6 ± 0.5	---	32.1 ± 0.2
94.00	---	59 ± 2	---	31.6 ± 0.2
96.00	---	57 ± 2	---	30.5 ± 0.9
98.00	---	54.5 ± 0.6	---	27.88 ± 0.06
100.00	2.5 ± 0.3	53.22 ± 0.01	---	26.2 ± 0.8

Initial pH of solutions

Table B.1.4. Initial pH of aqueous solution of biobased solvents at different concentrations.

wt %	CYR	GVL	HEX	PRO
0.00	6.11	6.11	6.11	6.11
1.00	4.28	3.85	6.24	6.05
2.00	4.02	3.59	5.65	5.21
3.00	3.99	3.52	5.7	6.25
4.00	3.78	3.41	5.43	4.57
5.00	3.71	3.37	5.37	5.94
12.00	3.44	3.24	5.06	6.11
20.00	3.22	3.16	5.35	6.11
30.00	3.1	3.22	5.4	5.93
40.00	3.01	3.37	5.57	5.11
50.00	2.96	3.52	5.63	6.33
60.00	2.89	3.65	5.9	6.48
70.00	2.77	3.91	6.81	6.57
80.00	2.63	4.21	6.68	6.34
90.00	2.79	4.57	6.59	6.38
100.00	--- [a]	--- [a]	--- [a]	--- [a]

[a]Data not measured

pH of saturated solutions

Table B.1.5. pH of aqueous solutions of biobased solvents after saturation with ferulic acid.

wt %	CYR	GVL	HEX	PRO
0.00	3.47	3.47	3.47	3.47
1.00	3.38	3.31	3.55	3.56
2.00	3.33	3.20	3.52	3.55
3.00	3.30	3.15	3.48	3.54
4.00	3.23	3.08	3.46	3.53
5.00	3.19	3.03	3.43	3.52
12.00	2.99	2.89	3.34	3.49
20.00	2.81	2.78	3.20	3.41
30.00	2.68	2.75	3.15	3.34
40.00	2.53	2.74	3.17	3.30
50.00	2.44	2.70	3.21	3.28
60.00	2.30	2.64	3.34	3.25
70.00	2.23	2.57	3.44	3.22
80.00	2.11	2.35	3.75	3.19
90.00	2.06	2.25	3.94	3.17
92.00	2.37	2.40	--- [a]	3.17
94.00	2.38	2.31	--- [a]	3.03
96.00	2.52	2.18	--- [a]	3.07
98.00	2.34	2.42	--- [a]	3.04
100.00	--- [a]	--- [a]	--- [a]	---- [a]

[a]Data not measured

Table B.1.6. pH of aqueous solutions of biobased solvents after saturation with syringic acid.

wt %	CYR	GVL	HEX	PRO
0.00	3.62	3.62	3.62	3.62
1.00	3.33	3.18	3.31	3.60
2.00	3.22	3.07	3.29	3.37
3.00	3.21	2.83	3.25	3.31
4.00	3.15	2.94	3.24	3.26
5.00	3.11	2.93	3.19	3.27
12.00	---[a]	2.84	---[a]	---[a]
20.00	---[a]	2.74	---[a]	---[a]
30.00	---[a]	2.67	---[a]	---[a]
40.00	---[a]	2.76	---[a]	---[a]
50.00	---[a]	2.76	---[a]	---[a]
60.00	---[a]	2.85	---[a]	---[a]
70.00	---[a]	2.83	---[a]	---[a]
80.00	2.56	2.89	---[a]	3.30
90.00	2.71	3.06	---[a]	3.50
92.00	2.59	3.10	---[a]	3.42
94.00	2.55	3.10	---[a]	3.79
96.00	2.58	3.06	---[a]	3.46
98.00	2.55	3.15	---[a]	3.55
100.00	2.84	---[a]	---[a]	3.43

[a]Data not measured

Table B.1.7. pH of aqueous solutions of biobased solvents after saturation with catechin.

wt %	CYR	GVL	HEX	PRO
0.00	3.47	3.47	3.47	3.47
1.00	3.72	3.41	4.10	4.07
2.00	3.51	3.26	3.88	4.11
3.00	3.40	3.21	3.85	4.22
4.00	2.26	3.12	3.72	3.93
5.00	2.07	3.02	3.68	4.21
12.00	3.00	2.95	3.60	3.84
20.00	2.31	2.80	3.56	3.64
30.00	2.56	2.79	3.63	3.55
40.00	2.71	2.74	3.63	3.52
50.00	2.59	2.71	3.70	3.68
60.00	2.61	2.63	4.07	3.82
70.00	2.55	2.50	4.32	4.00
80.00	---[a]	2.34	4.83	4.15
90.00	---[a]	2.37	4.60	4.37
92.00	---[a]	---[a]	---[a]	---[a]
94.00	---[a]	---[a]	---[a]	---[a]
96.00	---[a]	---[a]	---[a]	---[a]
98.00	---[a]	---[a]	---[a]	---[a]
100.00	---[a]	2.75	---[a]	4.74

[a]Data not measured

Setschenow constants

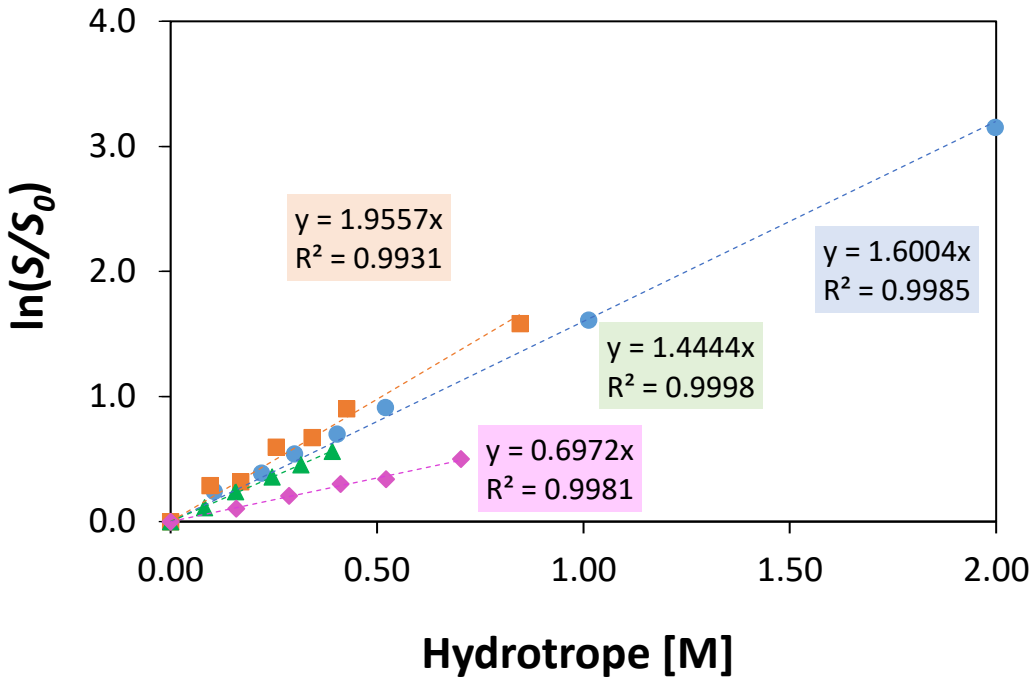

Figure B.1.1. Setschenow constant for ferulic acid in aqueous solutions of biobased solvents: (GVL (●), CYR (▲), HEX (■) and PRO (◆).

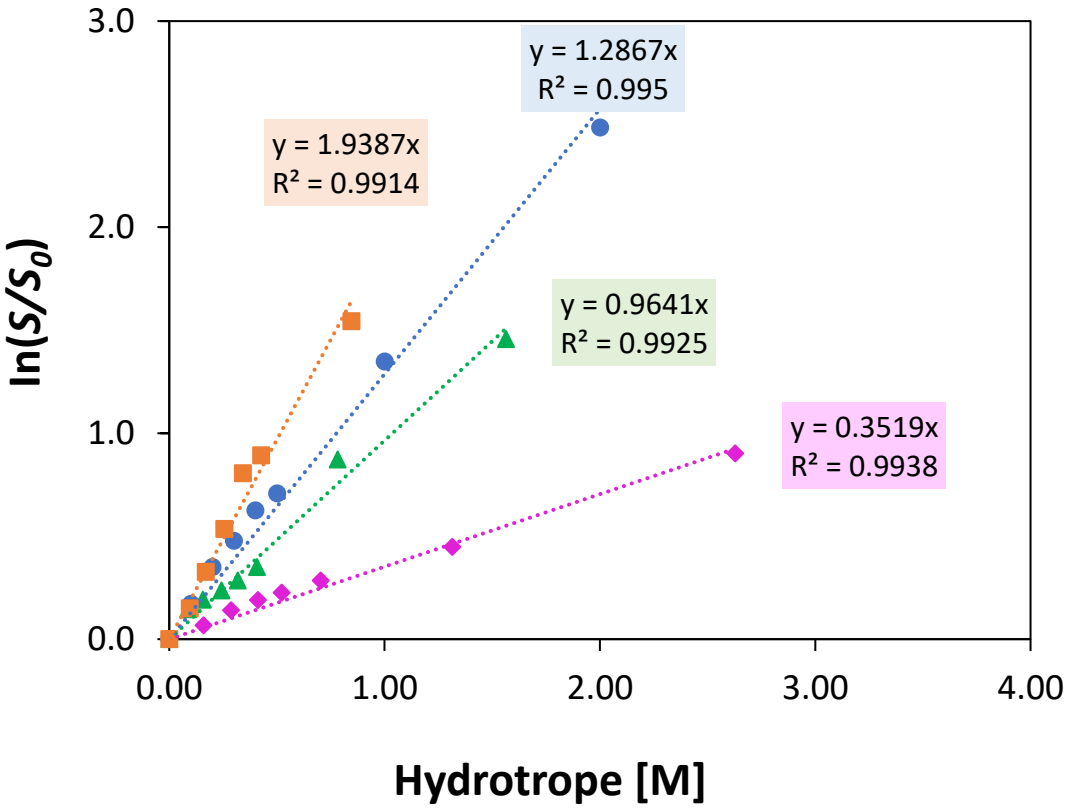

Figure B.1.2. Setschenow constant for syringic acid in aqueous solutions of biobased solvents: (GVL (●), CYR (▲), HEX (■) and PRO (◆).

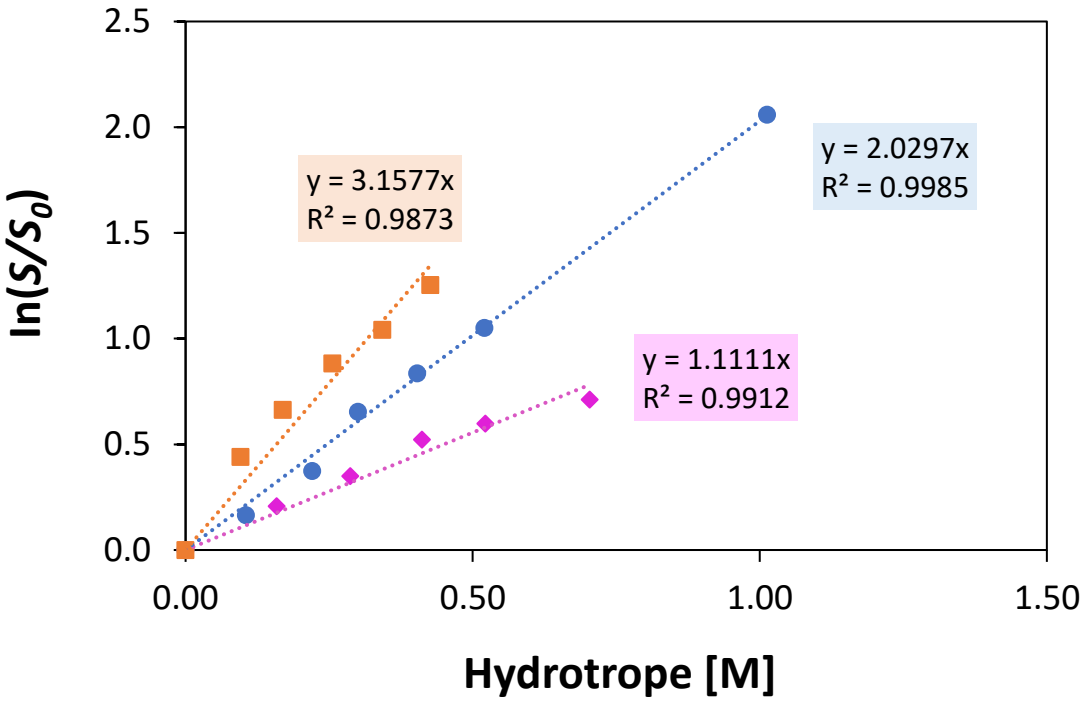

Figure B.1.3. Setschenow constant for catechin in aqueous solutions of biobased solvents: (GVL (●), HEX (■) and PRO (◆).

Cooperative model

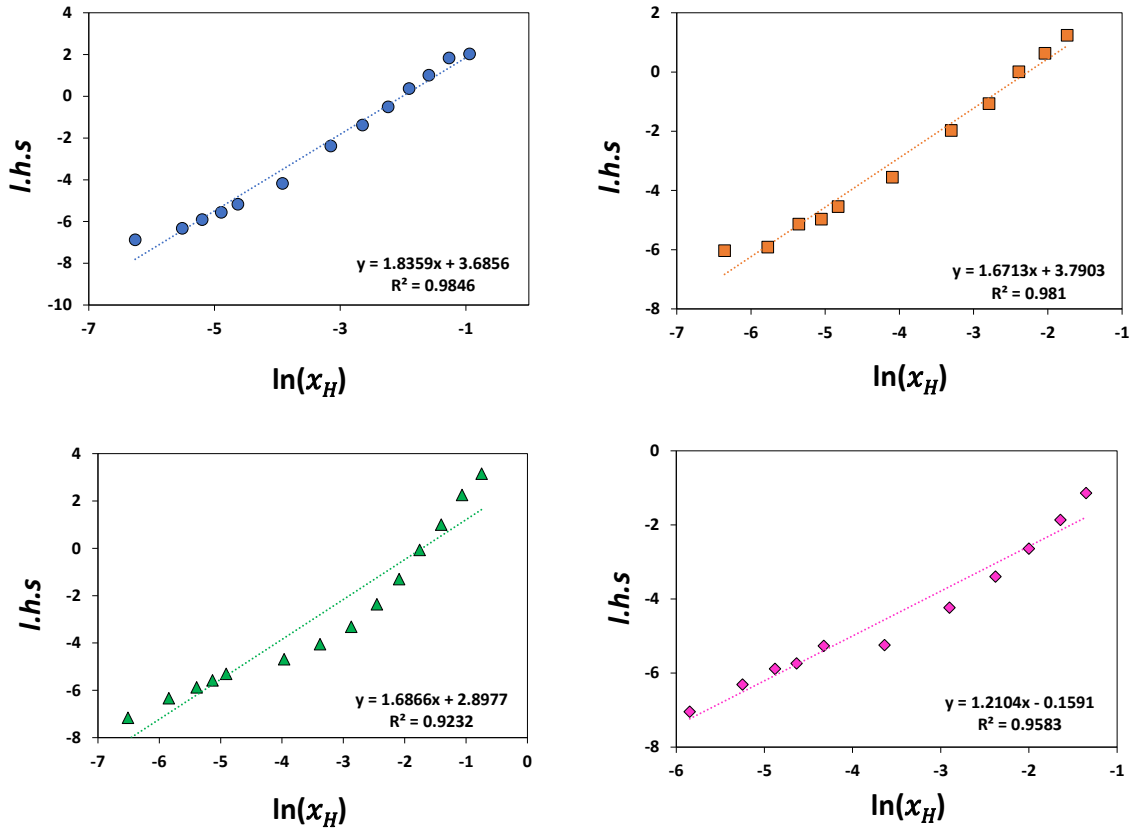

Figure B.1.4. Representation of the linearized plot of the cooperative model of ferulic acid in the presence of aqueous solutions of biobased solvents: GVL (●), HEX (■), CYR (▲) and PRO (◆). The y-axis is the left-hand side (*l.h.s.*) of Equation 5 as a function of the natural logarithm of hydrotrope mole fraction in the water/hydrotrope/solute at 30 °C. Dashed lines correspond to the best fitting obtained using the method of least squares.

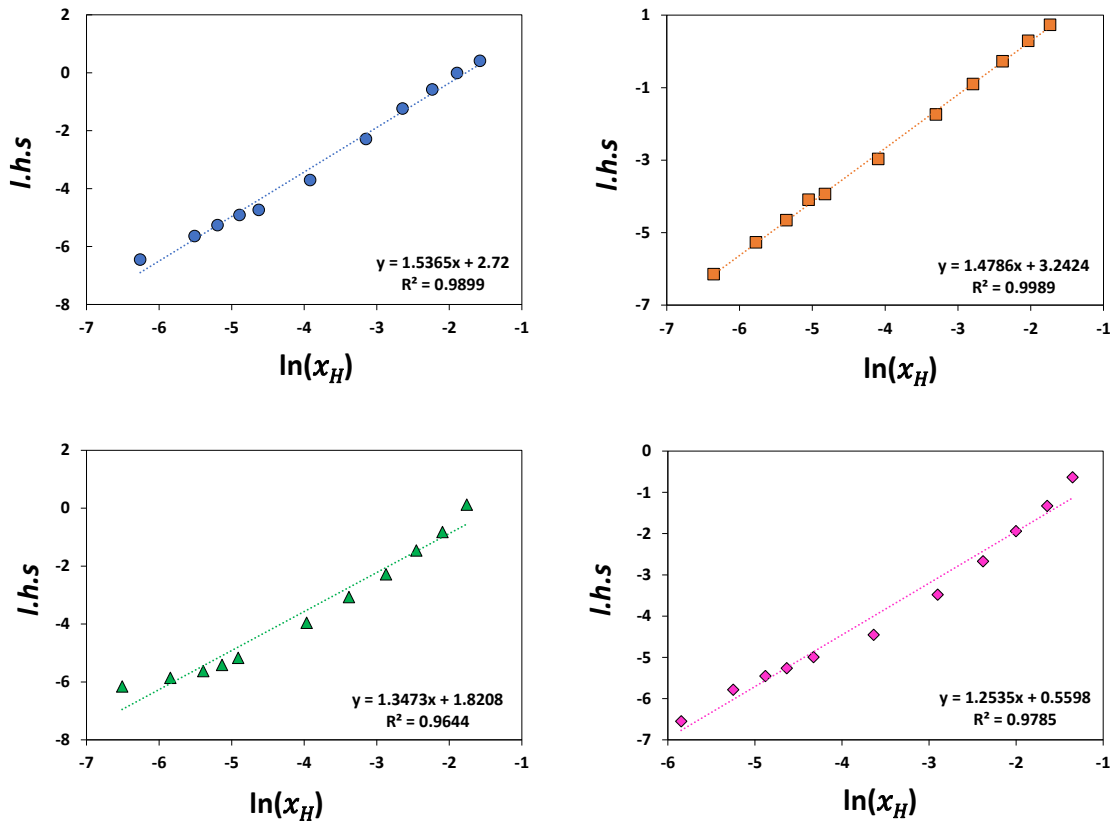

Figure B.1.5. Representation of the linearized plot of the cooperative model of syringic acid in the presence of aqueous solutions of biobased solvents: GVL (●), HEX (■), CYR (▲) and PRO (◆). The y-axis is the left-hand side (*l.h.s.*) of Equation 5 as a function of the natural logarithm of hydrotrope mole fraction in the water/hydrotrope/solute at 30 °C. Dashed lines correspond to the best fitting obtained using the method of least squares.

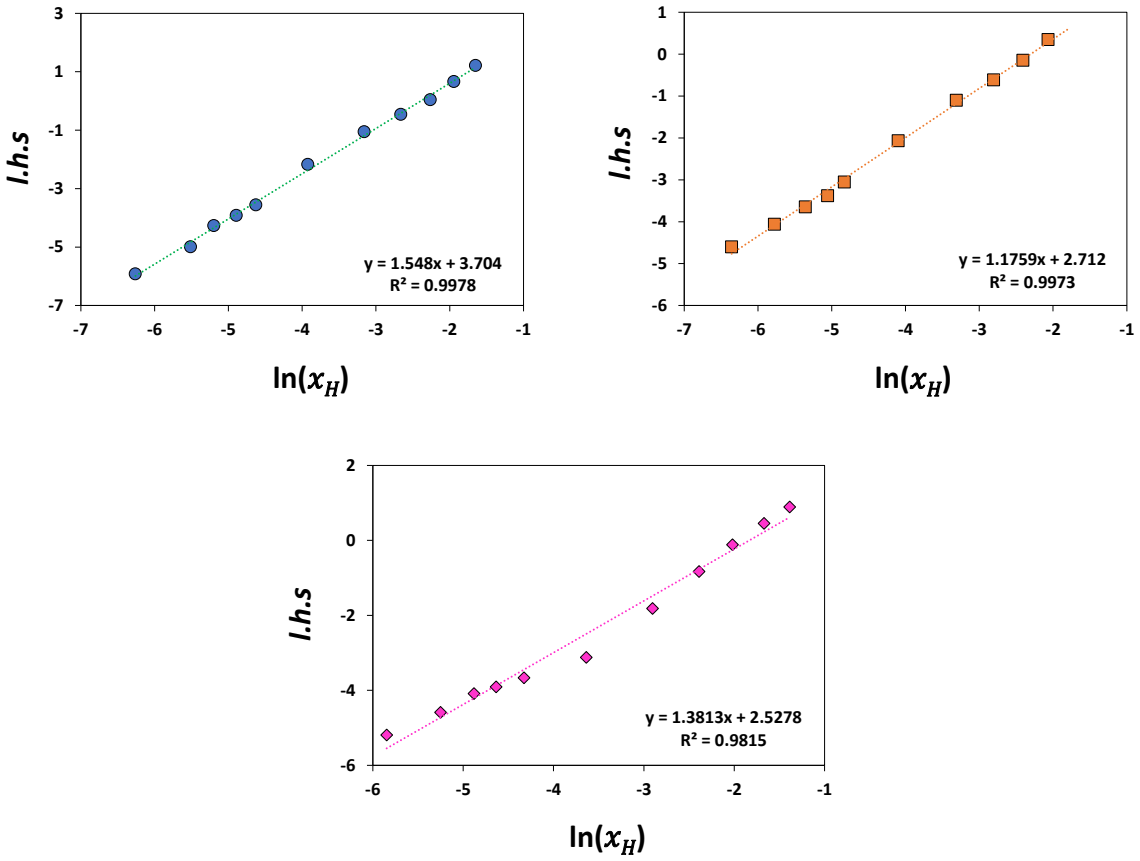

Figure B.1.6. Representation of the linearized plot of the cooperative model of catechin in the presence of aqueous solutions of biobased solvents: GVL (●), HEX (■), CYR (▲) and PRO (◆). The y-axis is the left-hand side (*l.h.s.*) of Equation 5 as a function of the natural logarithm of hydrotrope mole fraction in the water/hydrotrope/solute at 30 °C. Dashed lines correspond to the best fitting obtained using the method of least squares.

High pressure

Table B.1.8. Comparison of solubility of ferulic acid in different concentration of GVL (0%, 10%, 30% and 50%) realized at normal pressure in cells (1 bar, 1h, 2h, 3h, 4h and 24h) and in thermomixer (1 bar, 3 days), and at high pressure (100 bar, 2h and 24h) at 30 °C.

			[ferulic acid] (g/L)
Water	1 bar	1 h	0.63 ± 0.07
		2 h	0.71 ± 0.06
		3 h	0.78 ± 0.05
		4 h	0.80 ± 0.05
		24 h	0.84 ± 0.04
	Thermomixer	72 h	0.83 ± 0.05
	100 bar	2 h	0.84 ± 0.03
		24 h	0.85 ± 0.03
GVL 10%	1 bar	1 h	3.0 ± 0.1
		2 h	3.25 ± 0.02
		3 h	3.4 ± 0.2
		24 h	4.0 ± 0.4
	Thermomixer	72 h	4.18 ± 0.04
	100 bar	2 h	4.1 ± 0.4
		24 h	4.3 ± 0.6
GVL 30%	1 bar	1 h	32 ± 1
		2 h	34.87 ± 0.04
		3 h	35.5 ± 0.3
		24 h	39 ± 1
		48 h	42 ± 1
	Thermomixer	72 h	45 ± 2
	100 bar	2 h	44.7 ± 0.9
		24 h	45 ± 2
GVL 50%	1 bar	1 h	91 ± 4
		2 h	91 ± 3
		3 h	93 ± 5
		24 h	98 ± 5
		48 h	100 ± 3
	Thermomixer	72 h	132 ± 2
	100 bar	2 h	129 ± 5
		24 h	130 ± 1

B.2. Extraction of phenolic compounds from kiwi waste

Screening of biobased solvents for the extraction of phenolic compounds

Table B.2.1. Evaluation of the phenolic content (TPC) and the antioxidant activity (FRAP and ABTS) of the Kiwi peels extracts using conventional solvents (red), binary mixtures of biobased solvents with water (H_2O) or ethanol (EtOH) in the proportions of 3:7 and 7:3 (wt/wt), and ternary mixtures composed of biobased solvent, ethanol and water in the proportion of 4:4:2. Fixed extraction conditions: solid-liquid ratio of 0.05, during 60 min and at 25 °C, by CE.

Extraction solvent	TPC (mg GAE/g DW)	FRAP (mg TE/g DW)	ABTS (mg TE/g DW)
H_2O	2.1 ± 0.4	6 ± 1	4.4 ± 0.6
MeOH	6.4 ± 0.1	21 ± 1	22 ± 1
EtOH	5.4 ± 0.1	15 ± 2	14.3 ± 0.9
EtOH:H_2O (7:3)	8.8 ± 0.9	24 ± 1	25.0 ± 0.6
EtOH:H_2O (3:7)	5.2 ± 0.2	8.0 ± 0.5	5.1 ± 0.2
EtOH:H_2O at pH2 (7:3)	8.6 ± 0.9	24.7 ± 0.6	28.7 ± 0.5
EtOH:H_2O at pH2 (3:7)	5.2 ± 0.8	19.59 ± 0.06	22.9 ± 0.2
Acetone	14 ± 1	43 ± 2	55.1 ± 0.9
ETG:H_2O (7:3)	18 ± 2	45 ± 3	66 ± 5
ETG:H_2O (3:7)	9.9 ± 0.9	21.6 ± 0.3	34 ± 1
PRO:H_2O (7:3)	10.8 ± 0.4	23 ± 3	31.9 ± 0.5
PRO:H_2O (3:7)	3.9 ± 0.6	7.8 ± 0.2	20.4 ± 0.3
HEX:H_2O (7:3)	12.1 ± 0.5	28 ± 4	38 ± 4
HEX:H_2O (3:7)	8 ± 1	13.6 ± 0.8	22 ± 3
GVL:H_2O (7:3)	19 ± 1	40 ± 3	65.6 ± 0.9
GVL:H_2O (3:7)	12 ± 1	14.1 ± 0.1	23 ± 1
ETG:EtOH (7:3)	17.0 ± 0.6	43 ± 2	60 ± 3
ETG:EtOH (3:7)	11.3 ± 0.4	29 ± 2	39 ± 4
PRO:EtOH (7:3)	10.0 ± 0.5	30 ± 2	40 ± 2
PRO:EtOH (3:7)	6.7 ± 0.9	16.7 ± 0.8	25.0 ± 0.3
HEX:EtOH (7:3)	9.12 ± 0.01	28.2 ± 0.3	38 ± 2
HEX:EtOH (3:7)	6.3 ± 0.2	22 ± 1	22 ± 1
GVL:EtOH (7:3)	19 ± 1	47 ± 1	70 ± 2
GVL:EtOH (3:7)	11.9 ± 0.6	30.2 ± 0.4	40 ± 3
ETG:EtOH:H_2O (4:4:2)	18.7 ± 0.1	45 ± 3	64 ± 2
PRO:EtOH:H_2O (4:4:2)	10.8 ± 0.5	25 ± 2	41 ± 1
HEX:EtOH:H_2O (4:4:2)	10.0 ± 0.3	25.5 ± 0.7	38 ± 1
GVL:EtOH:H_2O (4:4:2)	19 ± 1	43 ± 2	62 ± 1

Table B.2.2. Initial pH of all solvents used in the screening of biosolvents for the extraction of phenolic compounds.

Extraction solvent	pH
EtOH:H_2O (7:3)	8.08 ± 0.01
EtOH:H_2O (3:7)	7.02 ± 0.01
GVL:H_2O (7:3)	3.62 ± 0.01
GVL:H_2O (3:7)	2.81 ± 0.02
ETG:H_2O (7:3)	5.93 ± 0.01
ETG:H_2O (3:7)	5.29 ± 0.03
PRO:H_2O (7:3)	6.06 ± 0.03
PRO:H_2O (3:7)	6.01 ± 0.01
HEX:H_2O (7:3)	6.20 ± 0.01
HEX:H_2O (3:7)	5.27 ± 0.01
GVL:EtOH:H_2O (4:4:2)	5.52 ± 0.01
ETG:EtOH:H_2O (4:4:2)	5.52 ± 0.01
PRO:EtOH:H_2O (4:4:2)	7.38 ± 0.02
HEX:EtOH:H_2O (4:4:2)	6.90 ± 0.01

Optimization of the solvent composition

Table B.2.3. Total phenolic content (TPC) of the extracts obtained from the design mixture composed of gamma-valerolactone, ethanol and water (GVL:EtOH:H_2O). Model: R^2 = 0.93 and R^2_{adj} = 0.88.

Real variables			TPC		
EtOH	GVL	H_2O	Experimental (mg GAE/g DW)	Predicted (mg GAE/g DW)	Relative deviation (%)
0.00	0.67	0.33	18.61	18.45	0.87
0.00	0.00	1.00	2.09	0.64	24.82
0.33	0.33	0.33	17.92	15.67	14.33
0.00	1.00	0.00	16.35	16.76	2.48
0.17	0.67	0.17	18.27	18.75	2.54
1.00	0.00	0.00	5.35	5.20	2.82
0.33	0.67	0.00	19.09	18.28	4.43
0.67	0.00	0.33	8.81	7.70	14.39
0.00	0.33	0.67	12.40	12.00	3.32
0.33	0.33	0.33	16.98	15.67	8.34
0.67	0.33	0.00	11.88	13.66	13.02
0.17	0.17	0.67	6.17	10.25	29.78
0.67	0.17	0.17	11.69	11.91	1.91
0.33	0.00	0.67	5.23	5.88	11.01

***** GAE: Gallic acid equivalent; DW: Dry weight

Table B.2.4. Antioxidant activity evaluated with FRAP assay of the extracts obtained from the design mixture composed of gamma-valerolactone, ethanol and water (GVL:EtOH:H_2O). Model: R^2 = 0.90 and R^2_{adj} = 0.84.

Real variables			FRAP		
EtOH	GVL	H_2O	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
0.00	0.67	0.33	40.07	35.55	12.71
0.00	0.00	1.00	5.58	-1.04	-34.57
0.33	0.33	0.33	35.46	33.98	4.35
0.00	1.00	0.00	38.81	41.60	6.71
0.17	0.67	0.17	43.27	41.77	3.59
1.00	0.00	0.00	11.70	13.17	11.18
0.33	0.67	0.00	47.13	46.47	1.42
0.67	0.00	0.33	23.90	19.14	24.86
0.00	0.33	0.67	14.12	18.50	23.69
0.33	0.33	0.33	37.26	33.98	9.64
0.67	0.33	0.00	30.18	35.10	14.01
0.17	0.17	0.67	11.77	19.19	28.69
0.67	0.17	0.17	32.58	28.94	12.60
0.33	0.00	0.67	7.98	13.45	40.69

***** TE: Trolox equivalent; DW: Dry weight

Table B.2.5. Antioxidant activity evaluated with ABTS assay of the extracts obtained from the design mixture composed of gamma-valerolactone, ethanol and water (GVL:EtOH:H_2O). Model: R^2 = 0.92 and R^2_{adj} = 0.86.

Real variables			ABTS		
EtOH	GVL	H_2O	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
0.00	0.67	0.33	65.61	55.65	17.91
0.00	0.00	1.00	4.37	-3.19	-37.18
0.33	0.33	0.33	52.58	46.14	13.94
0.00	1.00	0.00	53.67	58.51	8.28
0.17	0.67	0.17	54.59	60.16	9.26
1.00	0.00	0.00	14.25	14.48	1.60
0.33	0.67	0.00	69.77	63.81	9.33
0.67	0.00	0.33	25.04	18.26	37.10
0.00	0.33	0.67	23.10	30.97	25.41
0.33	0.33	0.33	48.60	46.14	5.33
0.67	0.33	0.00	40.47	46.20	12.39
0.17	0.17	0.67	18.80	25.57	26.46
0.67	0.17	0.17	33.47	35.54	5.82
0.33	0.00	0.67	5.13	11.19	54.20

* TE: Trolox equivalent; DW: Dry weight

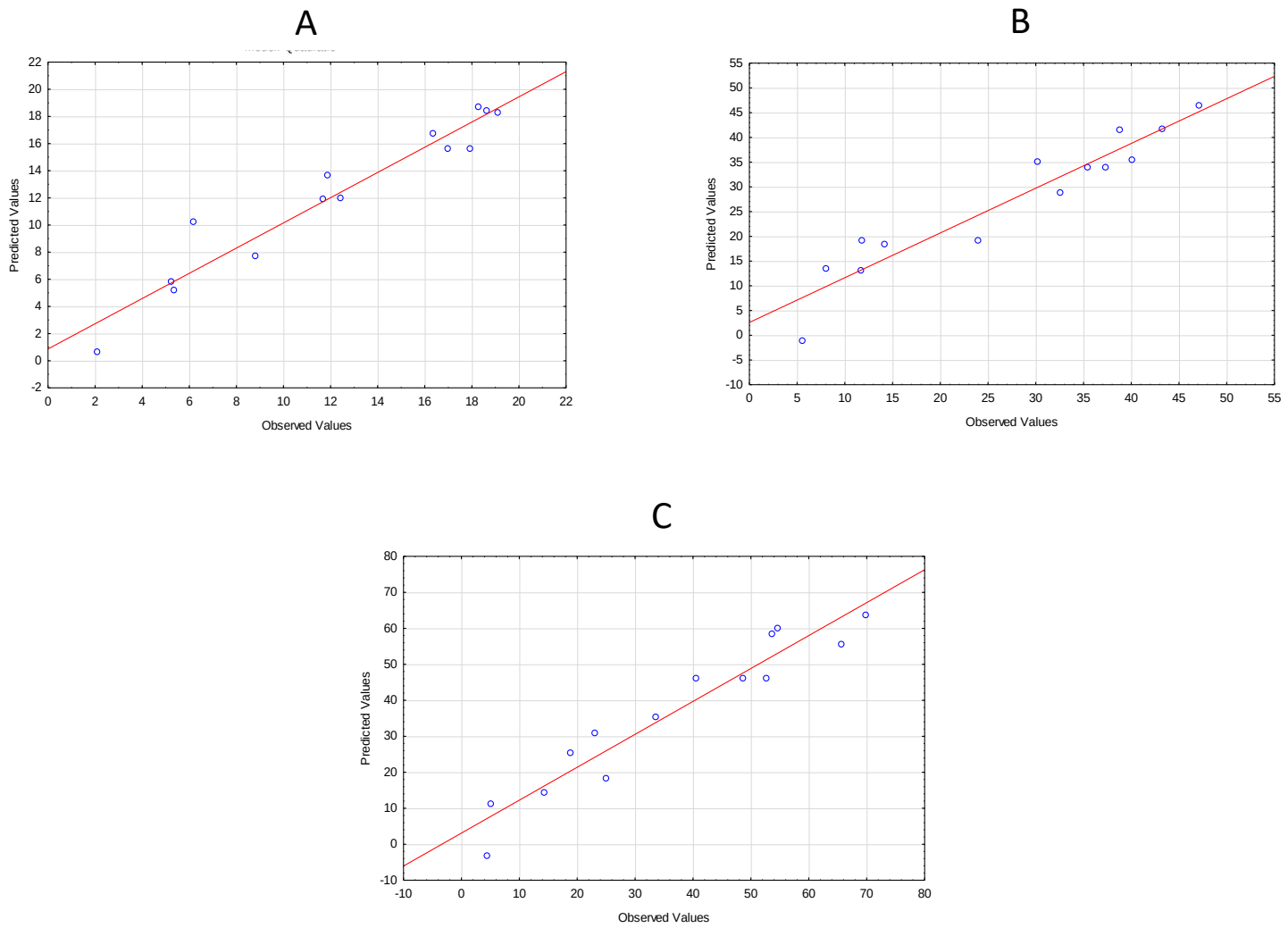

Figure B.2.1. Predict *vs.* observed values of (A) TPC, (B) FRAP and (C) ABTS from mixture design.

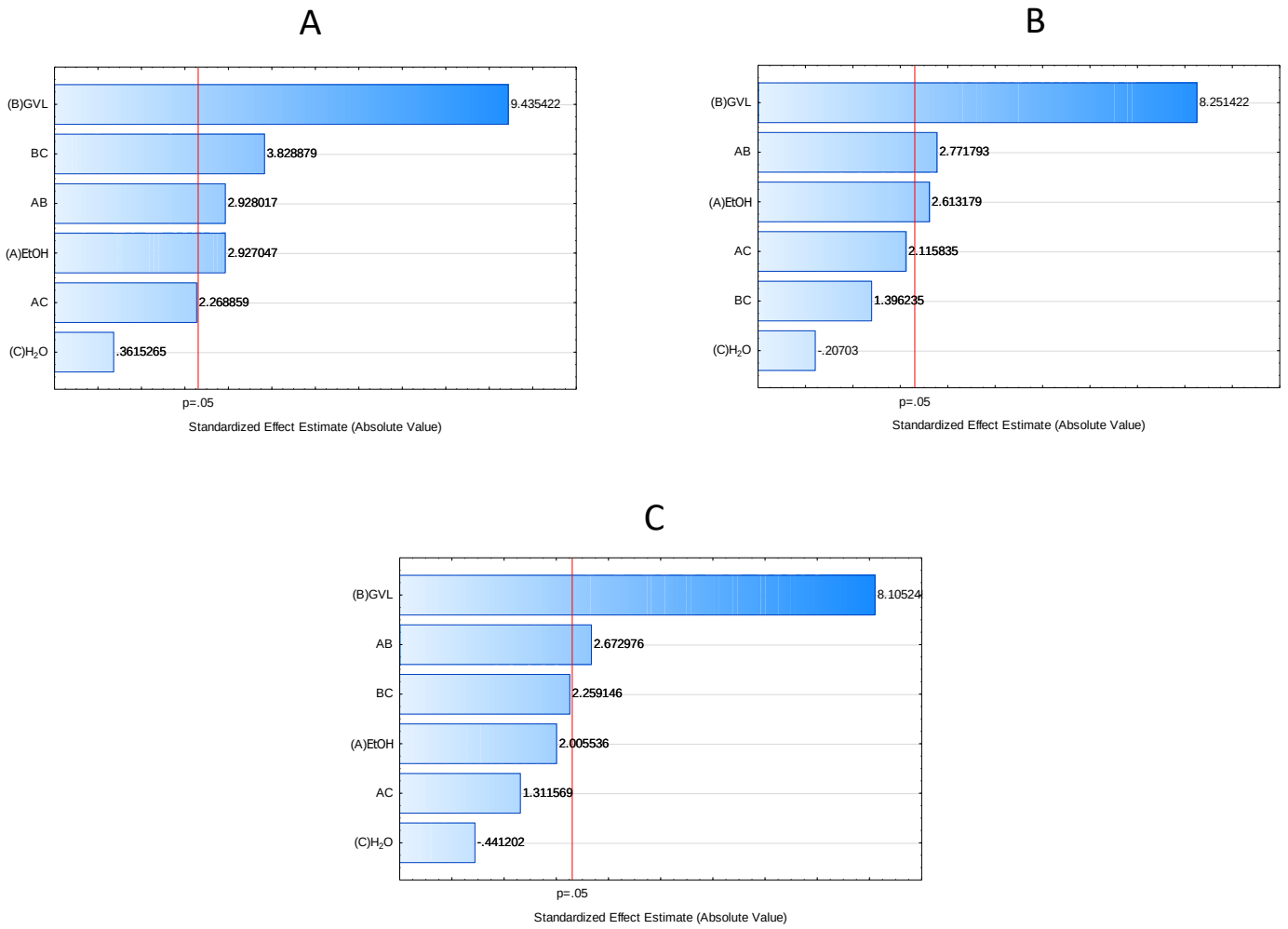

Figure B.2.2. Pareto charts for the standardized main effects in the mixture design for (A) TPC, (B) FRAP and (C) ABTS. The vertical line indicates the statistical significance of the effects (95% of confidence).

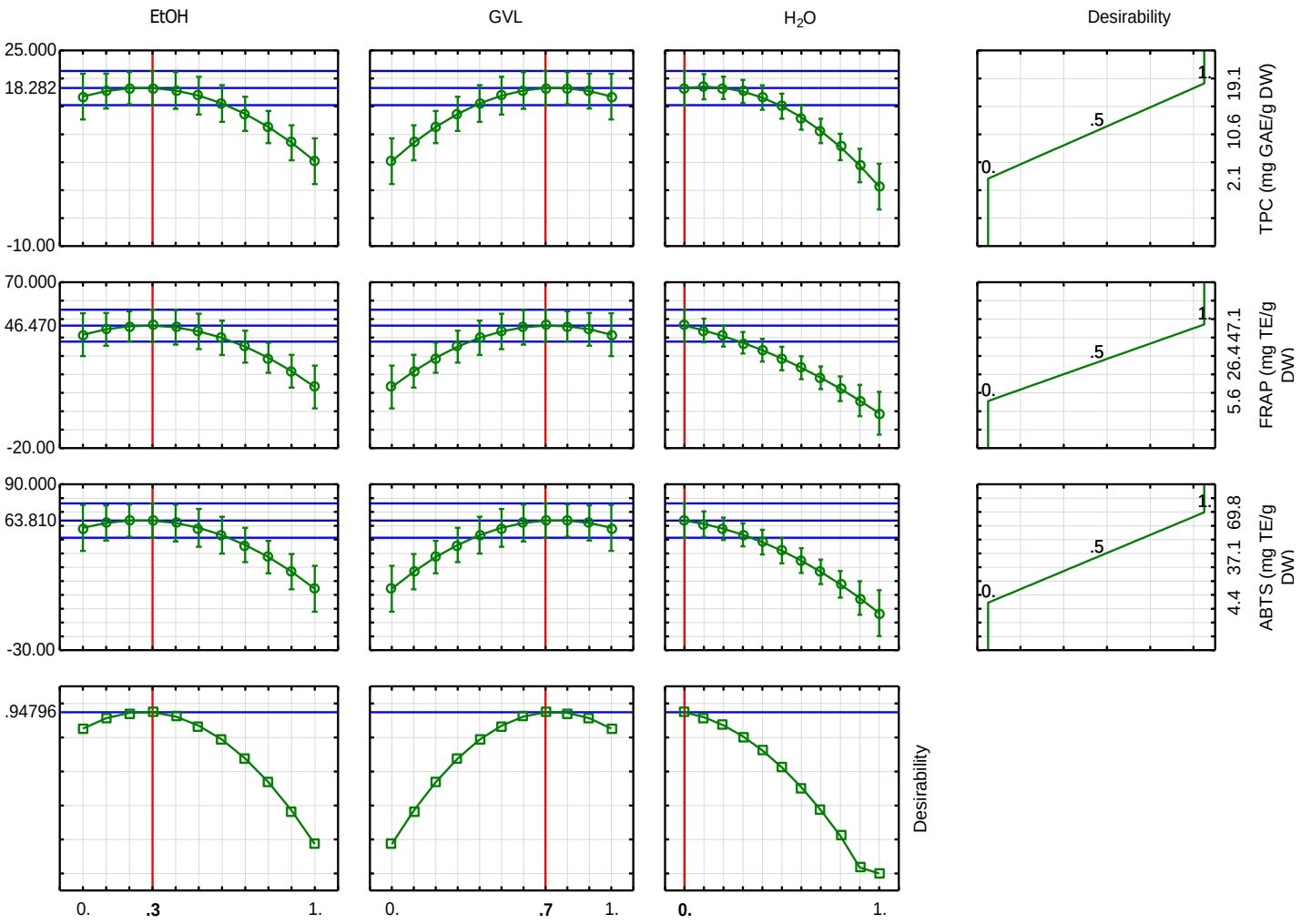

Figure B.2.3. Profiles for predicted values and desirability function for the TPC, FRAP and ABTS from mixture design. Red lines indicate optimized values for each component.

Optimization of the extraction conditions

Conventional extraction (CE)

Table B.2.6. Total phenolic content (TPC) of the extracts obtained by CE from the factorial planning.

Model: R^2 = 0.93 and R^2_{adj} = 0.87.

Real variables			TPC		
Temperature (ºC)	Time (min)	Solid-liquid ratio	Experimental (mg GAE/g DW)	Predicted (mg GAE/g DW)	Relative deviation (%)
30	30.0	0.030	18.19	18.07	0.62
50	30.0	0.030	16.12	15.71	2.64
30	90.0	0.030	20.54	20.12	2.10
50	90.0	0.030	16.14	16.74	3.58
30	30.0	0.070	20.61	20.13	2.37
50	30.0	0.070	18.40	18.94	2.88
30	90.0	0.070	21.23	21.77	2.46
50	90.0	0.070	19.34	19.57	1.20
23	60.0	0.050	19.24	19.58	1.74
57	60.0	0.050	16.26	15.75	3.28
40	9.5	0.050	17.86	18.19	1.82
40	110.4	0.050	20.95	20.44	2.48
40	60.0	0.016	17.51	17.78	1.49
40	60.0	0.084	22.37	21.93	1.98
40	60.0	0.050	19.75	20.00	1.26
40	60.0	0.050	20.41	20.00	2.07
40	60.0	0.050	19.54	20.00	2.28
40	60.0	0.050	20.79	20.00	3.94
40	60.0	0.050	20.06	20.00	0.30
40	60.0	0.050	19.42	20.00	2.91

***** GAE: Gallic acid equivalent; DW: Dry weight

Table B.2.7. Antioxidant activity evaluated with FRAP assay of the extracts obtained by CE from the factorial planning. Model: R^2 = 0.95 and R^2_{adj} = 0.90.

Real variables			FRAP		
Temperature (ºC)	Time (min)	Solid-liquid ratio	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
30	30.0	0.030	40.53	38.84	4.37
50	30.0	0.030	36.10	35.33	2.18
30	90.0	0.030	40.88	39.05	4.68
50	90.0	0.030	36.92	37.10	0.51
30	30.0	0.070	55.29	54.02	2.36
50	30.0	0.070	44.58	45.32	1.64
30	90.0	0.070	58.24	57.92	0.54
50	90.0	0.070	50.17	50.78	1.20
23	60.0	0.050	46.35	48.86	5.15
57	60.0	0.050	40.91	39.93	2.46
40	9.5	0.050	42.11	43.38	2.91
40	110.4	0.050	47.87	48.15	0.57
40	60.0	0.016	30.64	32.53	5.81
40	60.0	0.084	57.45	57.06	0.68
40	60.0	0.050	47.44	48.54	2.25
40	60.0	0.050	49.47	48.54	1.92
40	60.0	0.050	45.53	48.54	6.19
40	60.0	0.050	49.64	48.54	2.28
40	60.0	0.050	52.40	48.54	7.95
40	60.0	0.050	46.97	48.54	3.23

***** TE: Trolox equivalent; DW: Dry weight

Table B.2.8. Antioxidant activity evaluated with ABTS assay of the extracts obtained by CE from the factorial planning. Model: R^2 = 0.94 and R^2_{adj} = 0.88.

Real variables			ABTS		
Temperature (ºC)	Time (min)	Solid-liquid ratio	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
30	30.0	0.030	71.31	70.62	0.98
50	30.0	0.030	60.92	59.65	2.14
30	90.0	0.030	78.39	77.94	0.58
50	90.0	0.030	67.92	68.62	1.02
30	30.0	0.070	85.46	85.98	0.61
50	30.0	0.070	79.99	81.66	2.05
30	90.0	0.070	82.58	85.08	2.94
50	90.0	0.070	80.49	82.41	2.33
23	60.0	0.050	82.50	81.98	0.64
57	60.0	0.050	71.74	70.53	1.71
40	9.5	0.050	72.07	72.52	0.62
40	110.4	0.050	81.50	79.32	2.75
40	60.0	0.016	64.46	66.07	2.43
40	60.0	0.084	94.15	90.85	3.63
40	60.0	0.050	82.59	83.75	1.39
40	60.0	0.050	82.62	83.75	1.35
40	60.0	0.050	79.25	83.75	5.37
40	60.0	0.050	85.64	83.75	2.25
40	60.0	0.050	88.39	83.75	5.54
40	60.0	0.050	83.75	83.75	0.00

***** TE: Trolox equivalent; DW: Dry weight

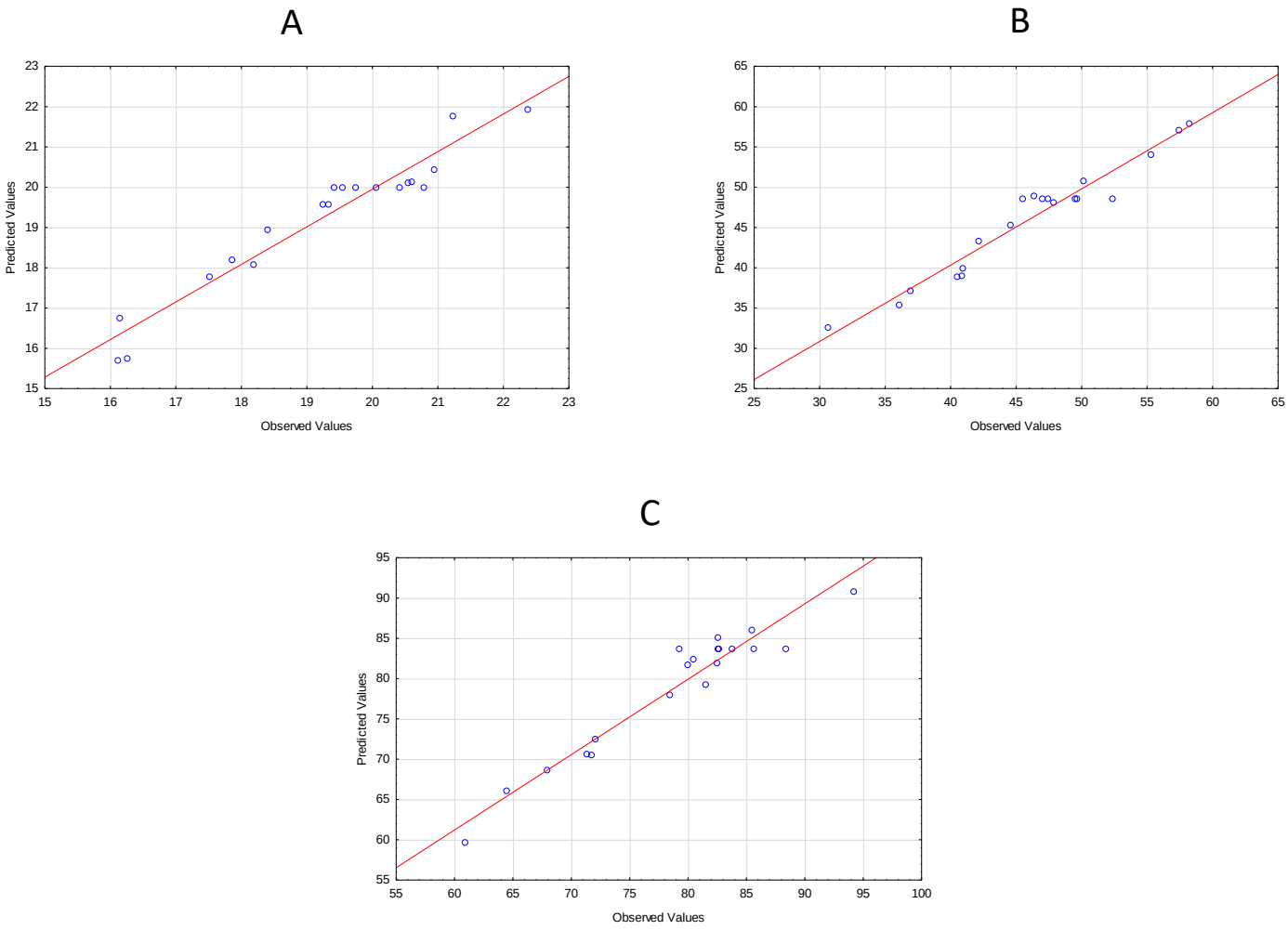

Figure B.2.4. Predict *vs.* observed values of (A) TPC, (B) FRAP and (C) ABTS for the extracts obtained by CE from the factorial planning.

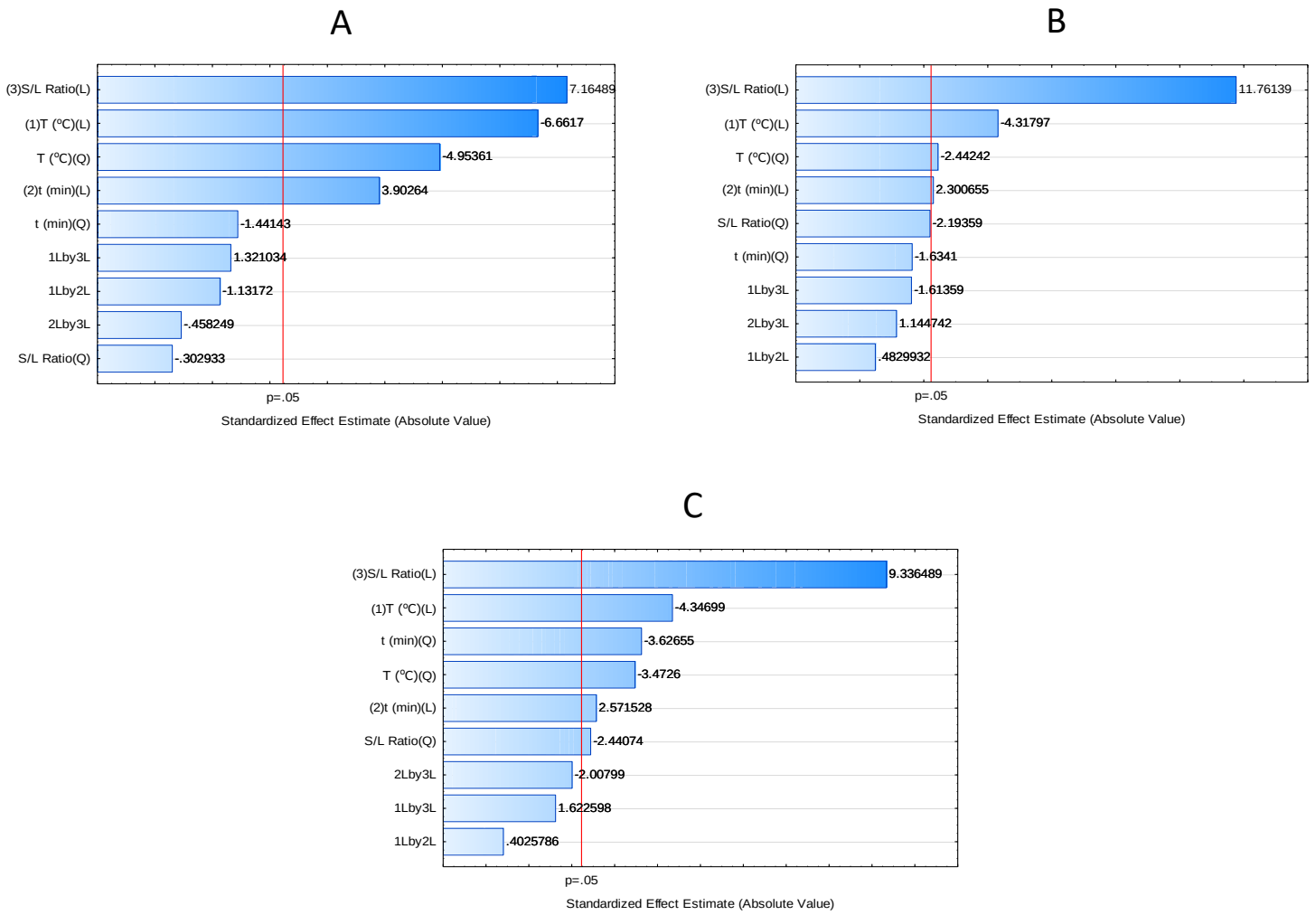

Figure B.2.5. Pareto charts for the standardized main effects in the factorial planning for (A) TPC, (B) FRAP and (C) ABTS, for the extracts obtained by CE. The vertical line indicates the statistical significance of the effects (95% of confidence).

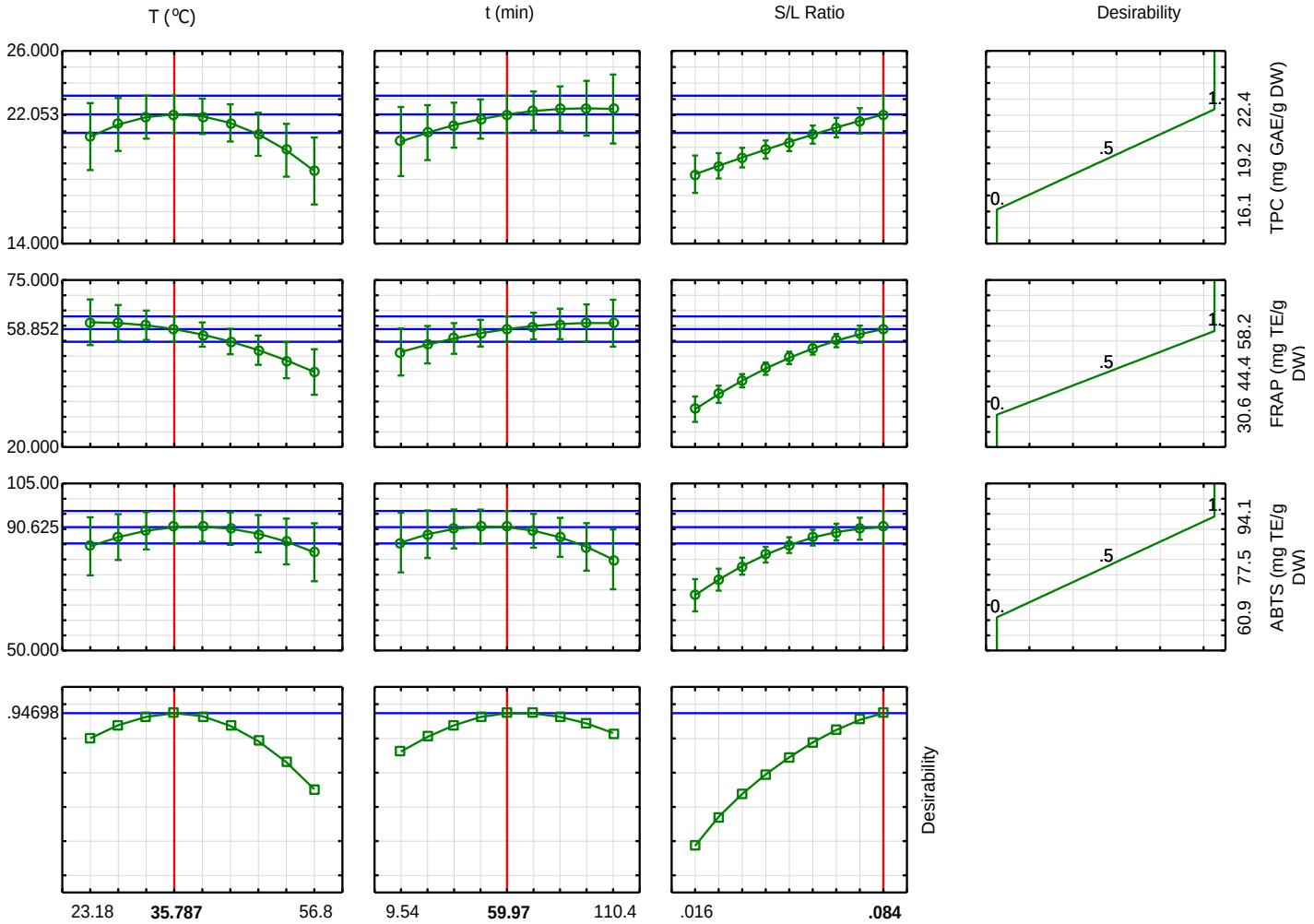

Figure B.2.6. Profiles for predicted values and desirability function for the TPC, FRAP and ABTS for the extracts obtained by CE from the factorial planning. Red lines indicate optimized values for each variable.

Table B.2.9. Corresponding values of TPC, FRAP and ABTS obtained using the optimal conventional extraction conditions (36 °C, 60 min) and applying different values of solid-liquid ratio (S/L Ratio).

S/L Ratio	TPC (mg GAE/g DW)	FRAP (mg TE/g DW)	ABTS (mg TE/g DW)
0.080	21 ± 3	61 ± 5	99.5 ± 0.8
0.010	21 ± 3	56 ± 6	91 ± 7
0.012	22 ± 2	56 ± 2	93 ± 4

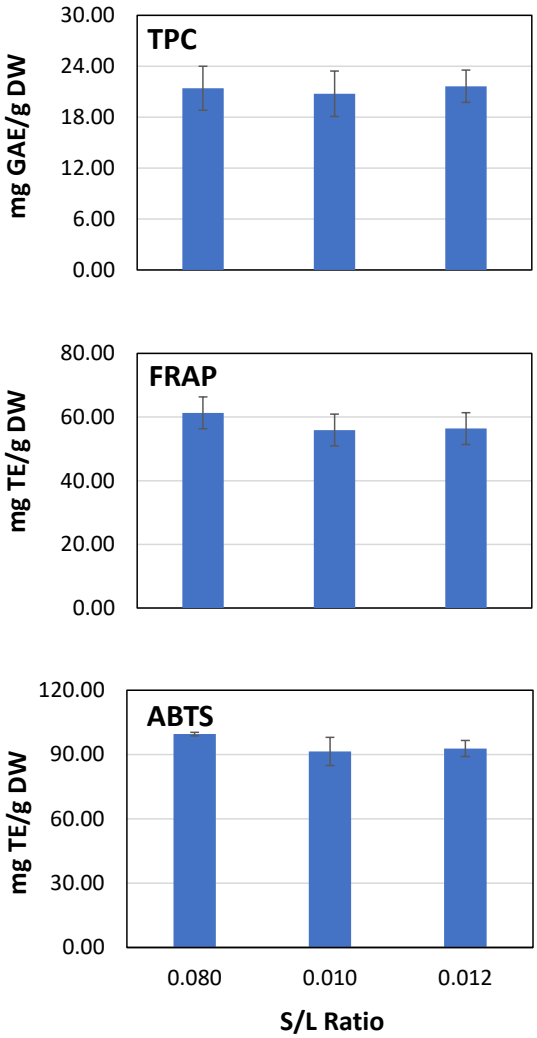

Figure B.2.7. Levels of TPC, FRAP and ABTS obtained using the optimal conventional extraction conditions (36 °C, 60 min) and applying different values of solid-liquid ratio (S/L Ratio).

Ultrasound-assisted extraction (UAE)

Table B.2.10. Total phenolic content (TPC) of the extracts obtained by UAE from the factorial planning.

Model: R^2 = 0.89 and R^2_{adj} = 0.79.

Real variables			TPC		
Amplitude (%)	Time (min)	Solid-liquid ratio	Experimental (mg GAE/g DW)	Predicted (mg GAE/g DW)	Relative deviation (%)
14	4.0	0.030	21.08	20.40	3.34
26	4.0	0.030	21.45	20.30	5.67
14	12.0	0.030	20.43	19.18	6.51
26	12.0	0.030	20.28	19.52	3.89
14	4.0	0.090	19.71	19.60	0.55
26	4.0	0.090	20.23	20.61	1.86
14	12.0	0.090	23.43	23.71	1.20
26	12.0	0.090	25.35	25.16	0.74
10	8.0	0.060	22.79	23.43	2.71
30	8.0	0.060	23.94	24.56	2.49
20	1.3	0.060	18.99	19.50	2.60
20	14.7	0.060	21.59	22.31	3.22
20	8.0	0.010	15.02	16.91	11.17
20	8.0	0.110	21.58	20.94	3.06
20	8.0	0.060	23.17	24.18	4.18
20	8.0	0.060	24.83	24.18	2.69
20	8.0	0.060	23.40	24.18	3.25
20	8.0	0.060	23.86	24.18	1.31
20	8.0	0.060	24.70	24.18	2.13
20	8.0	0.060	25.38	24.18	4.97

***** GAE: Gallic acid equivalent; DW: Dry weight

Table B.2.11. Antioxidant activity evaluated with FRAP assay of the extracts obtained by UAE from the factorial planning. Model: R^2 = 0.98 and R^2_{adj} = 0.96.

Real variables			FRAP		
Amplitude (%)	Time (min)	Solid-liquid ratio	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
14	4.0	0.030	56.37	55.80	1.03
26	4.0	0.030	73.82	75.52	2.26
14	12.0	0.030	60.75	63.32	4.05
26	12.0	0.030	73.24	72.46	1.08
14	4.0	0.090	53.23	54.79	2.85
26	4.0	0.090	68.32	66.53	2.68
14	12.0	0.090	80.93	80.01	1.15
26	12.0	0.090	79.82	81.18	1.67
10	8.0	0.060	65.48	64.28	1.87
30	8.0	0.060	81.61	81.69	0.10
20	1.3	0.060	58.58	58.42	0.28
20	14.7	0.060	78.01	77.07	1.22
20	8.0	0.010	65.00	63.63	2.16
20	8.0	0.110	69.80	70.05	0.36
20	8.0	0.060	74.88	75.94	1.39
20	8.0	0.060	78.09	75.94	2.84
20	8.0	0.060	76.39	75.94	0.59
20	8.0	0.060	74.50	75.94	1.89
20	8.0	0.060	76.05	75.94	0.15
20	8.0	0.060	75.48	75.94	0.60

* TE: Trolox equivalent; DW: Dry weight

Table B.2.12. Antioxidant activity evaluated with ABTS assay of the extracts obtained by UAE from the factorial planning. Model: R^2 = 0.91 and R^2_{adj} = 0.83.

Real variables			ABTS		
Amplitude (%)	**Time (min)**	**Solid-liquid ratio**	**Experimental (mg TE/g DW)**	**Predicted (mg TE/g DW)**	**Relative deviation (%)**
14	4.0	0.030	92.87	91.59	1.39
26	4.0	0.030	98.26	94.70	3.75
14	12.0	0.030	100.14	99.54	0.60
26	12.0	0.030	100.08	99.27	0.82
14	4.0	0.090	78.66	77.21	1.89
26	4.0	0.090	93.88	92.21	1.81
14	12.0	0.090	86.85	88.14	1.46
26	12.0	0.090	100.76	99.76	1.00
10	8.0	0.060	95.17	95.31	0.14
30	8.0	0.060	104.46	107.59	2.91
20	1.3	0.060	81.71	85.34	4.26
20	14.7	0.060	98.80	98.37	0.44
20	8.0	0.010	88.31	90.96	2.92
20	8.0	0.110	78.77	79.38	0.77
20	8.0	0.060	90.29	93.25	3.17
20	8.0	0.060	91.49	93.25	1.90
20	8.0	0.060	93.22	93.25	0.04
20	8.0	0.060	91.79	93.25	1.58
20	8.0	0.060	96.73	93.25	3.73
20	8.0	0.060	96.68	93.25	3.67

***** TE: Trolox equivalent; DW: Dry weight.

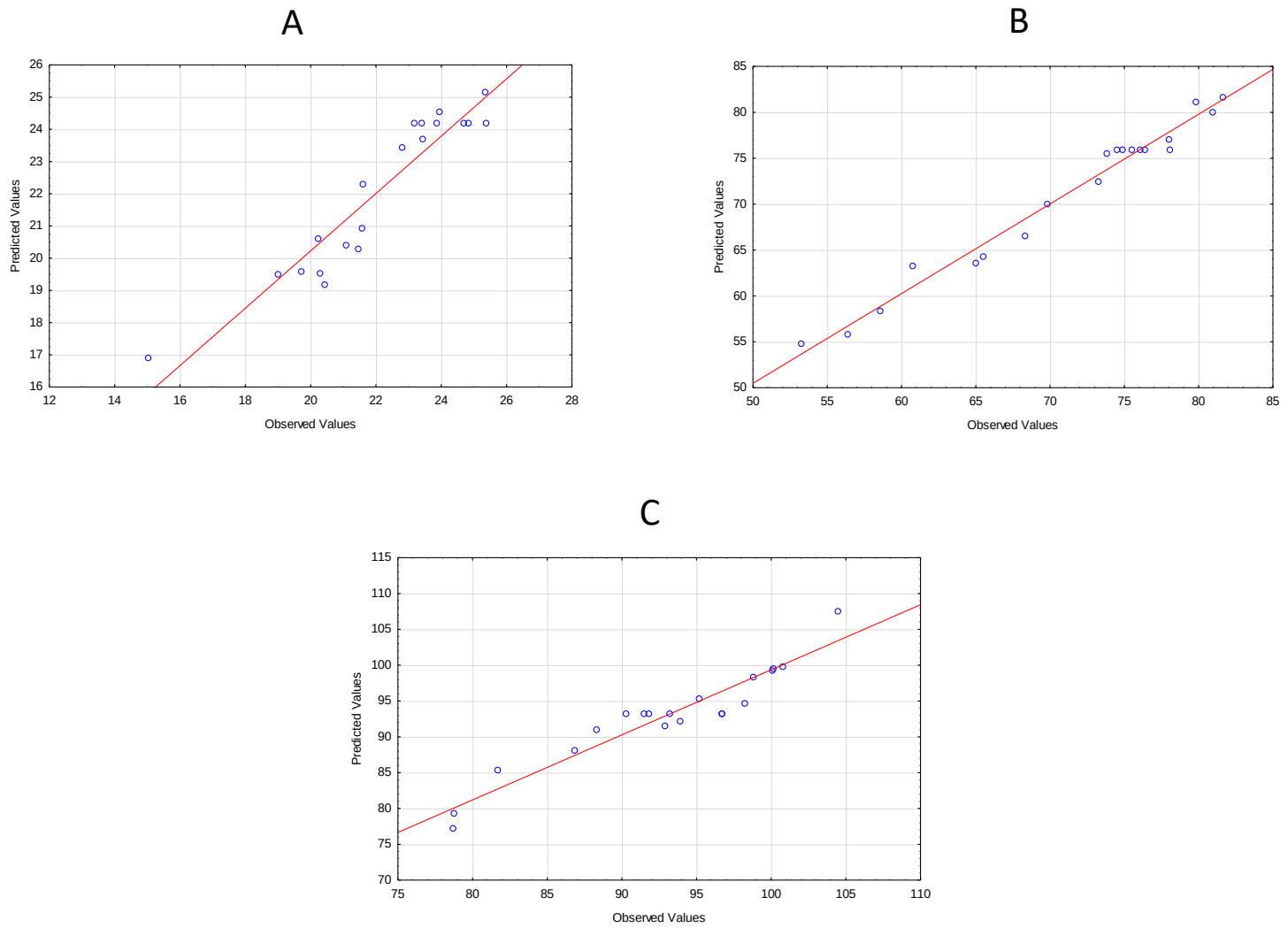

Figure B.2.8. Predict *vs.* observed values of (A) TPC, (B) FRAP and (C) ABTS for the extracts obtained by UAE from the factorial planning.

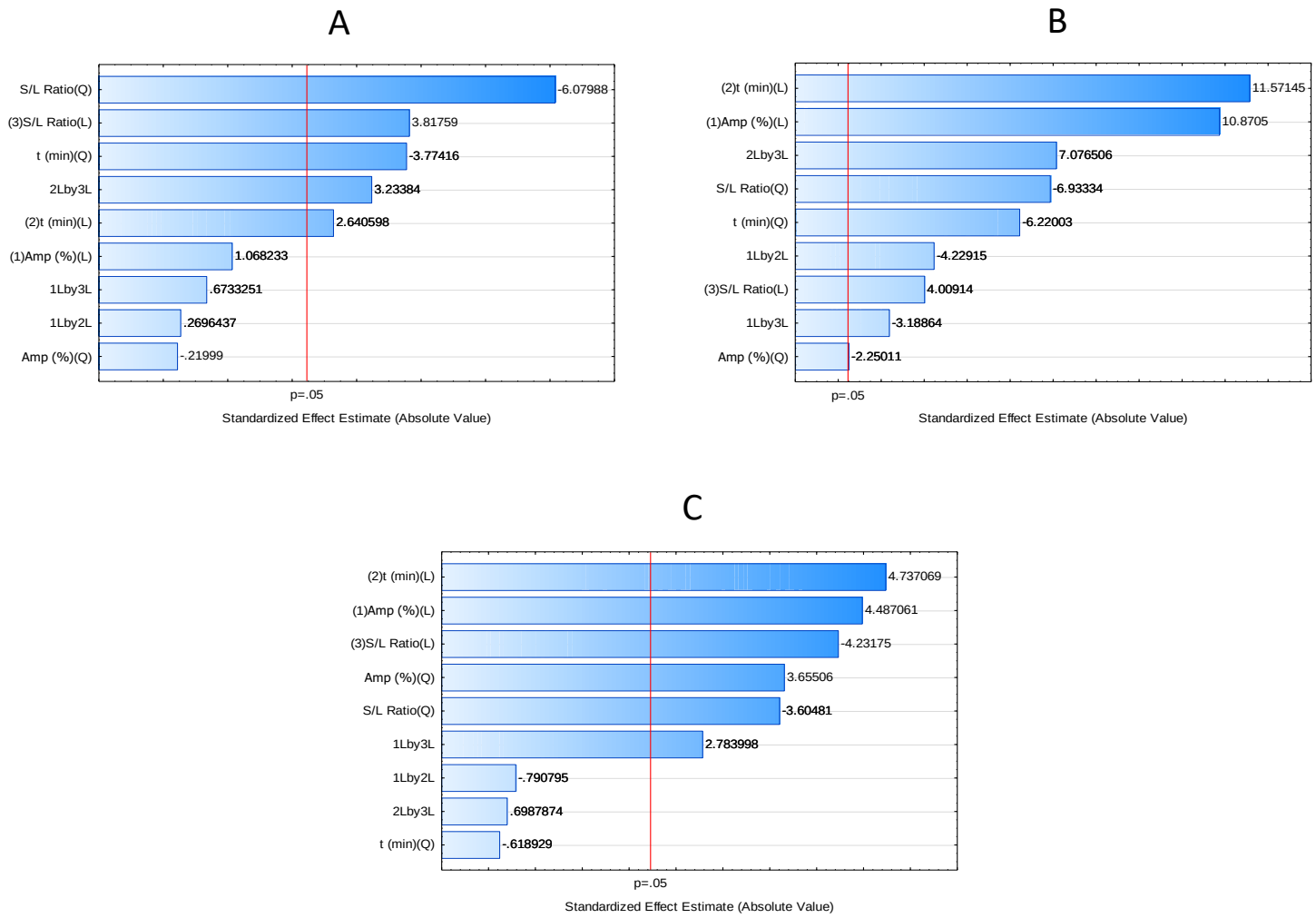

Figure B.2.9. Pareto charts for the standardized main effects in the factorial plannings for (A) TPC, (B) FRAP and (C) ABTS, for the extracts obtained by UAE. The vertical line indicates the statistical significance of the effects (95% of confidence).

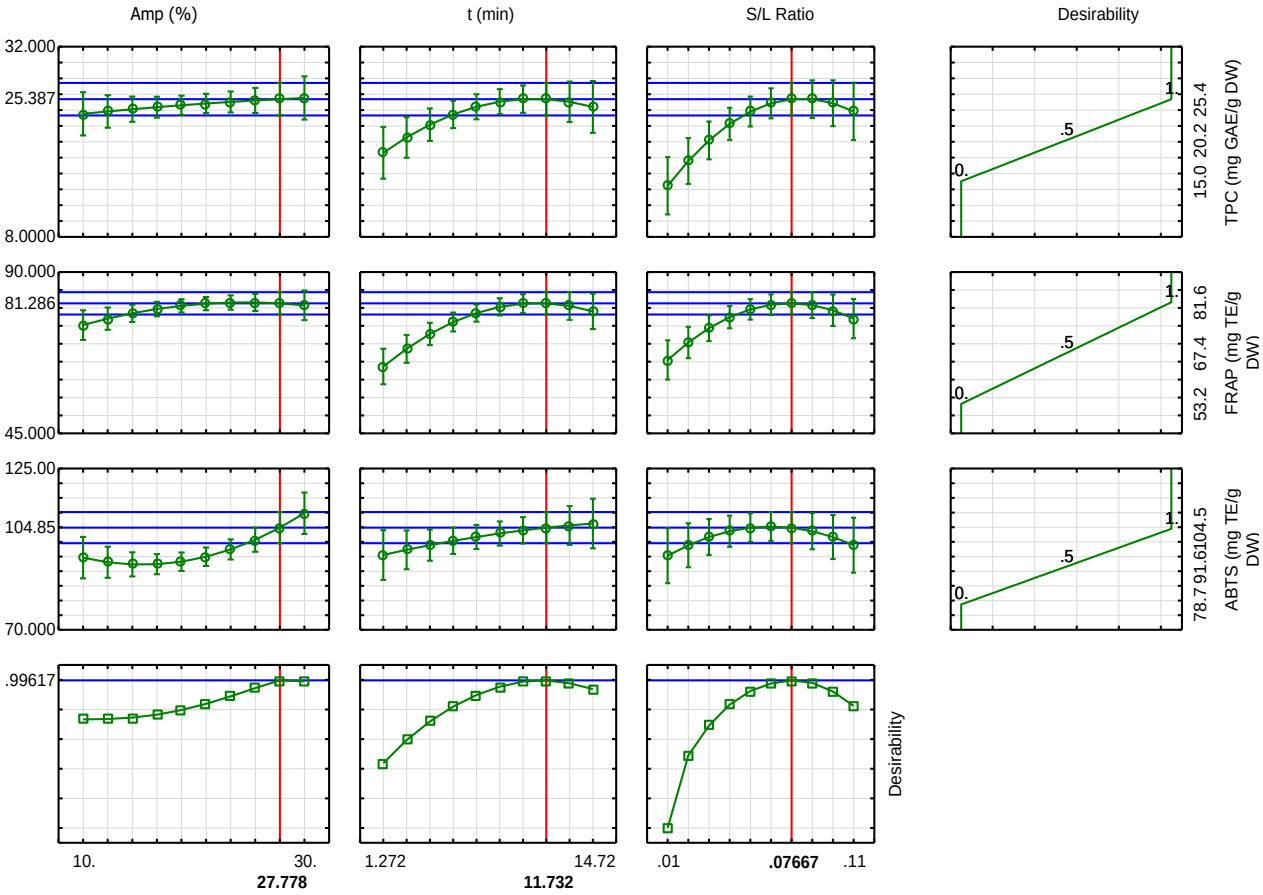

Figure B.2.10. Profiles for predicted values and desirability function for the TPC, FRAP and ABTS for the extracts obtained by UAE from the factorial planning. Red lines indicate optimized values for each variable

Microwave assisted extraction (MAE)

Table B.2.13. Total phenolic content (TPC) of the extracts obtained by MAE from factorial the planning.

Model: R^2 = 0.93 and R^2_{adj} = 0.87.

Real variables			TPC		
Temperature (ºC)	Time (min)	Solid-liquid ratio	Experimental (mg GAE/g DW)	Predicted (mg GAE/g DW)	Relative deviation (%)
58	3.0	0.030	26.44	25.89	2.13
82	3.0	0.030	20.16	18.67	7.99
58	9.0	0.030	25.25	24.42	3.40
82	9.0	0.030	16.16	16.73	3.40
58	3.0	0.090	25.05	24.23	3.36
82	3.0	0.090	24.80	25.39	2.32
58	9.0	0.090	23.72	24.98	5.02
82	9.0	0.090	25.35	25.66	1.21
50	6.0	0.060	29.55	30.00	1.50
90	6.0	0.060	24.59	24.50	0.39
70	1.0	0.060	18.99	20.22	6.10
70	11.0	0.060	20.14	19.24	4.68
70	6.0	0.010	19.09	20.34	6.16
70	6.0	0.110	27.38	26.47	3.45
70	6.0	0.060	26.67	26.92	0.93
70	6.0	0.060	28.91	26.92	7.41
70	6.0	0.060	26.00	26.92	3.42
70	6.0	0.060	27.45	26.92	1.98
70	6.0	0.060	26.27	26.92	2.42
70	6.0	0.060	26.28	26.92	2.36

***** GAE: Gallic acid equivalent; DW: Dry weight

Table B.2.14. Antioxidant activity evaluated with FRAP assay of the extracts obtained by MAE from the factorial planning. Model: R^2 = 0.98 and R^2_{adj} = 0.97.

Real variables			FRAP		
Temperature (ºC)	Time (min)	Solid-liquid ratio	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
58	3.0	0.030	71.59	71.34	0.35
82	3.0	0.030	59.39	58.20	2.04
58	9.0	0.030	75.08	73.39	2.30
82	9.0	0.030	54.34	55.02	1.23
58	3.0	0.090	73.67	73.38	0.39
82	3.0	0.090	72.79	74.88	2.79
58	9.0	0.090	77.70	79.28	2.00
82	9.0	0.090	74.89	75.54	0.86
50	6.0	0.060	87.63	88.20	0.65
90	6.0	0.060	75.15	74.02	1.53
70	1.0	0.060	58.42	58.39	0.04
70	11.0	0.060	61.26	60.72	0.88
70	6.0	0.010	60.68	62.33	2.64
70	6.0	0.110	83.53	81.32	2.72
70	6.0	0.060	81.54	82.24	0.86
70	6.0	0.060	82.78	82.24	0.65
70	6.0	0.060	84.26	82.24	2.46
70	6.0	0.060	82.81	82.24	0.69
70	6.0	0.060	81.71	82.24	0.64
70	6.0	0.060	80.23	82.24	2.44

***** TE: Trolox equivalent; DW: Dry weight

Table B.2.15. Antioxidant activity evaluated with ABTS assay of the extracts obtained by MAE from the factorial planning. Model: R^2 = 0.94 and R^2_{adj} = 0.89.

Real variables			ABTS		
Temperature (ºC)	Time (min)	Solid-liquid ratio	Experimental (mg TE/g DW)	Predicted (mg TE/g DW)	Relative deviation (%)
58	3.0	0.030	111.88	110.04	1.67
82	3.0	0.030	83.45	79.99	4.33
58	9.0	0.030	119.04	112.56	5.76
82	9.0	0.030	78.35	80.93	3.19
58	3.0	0.090	112.86	109.53	3.03
82	3.0	0.090	102.51	108.24	5.30
58	9.0	0.090	113.10	115.82	2.35
82	9.0	0.090	111.85	112.95	0.97
50	6.0	0.060	133.32	138.27	3.58
90	6.0	0.060	114.47	110.57	3.53
70	1.0	0.060	82.41	83.77	1.62
70	11.0	0.060	90.21	89.90	0.35
70	6.0	0.010	82.62	87.72	5.82
70	6.0	0.110	118.29	114.22	3.56
70	6.0	0.060	106.92	109.22	2.11
70	6.0	0.060	112.50	109.22	3.00
70	6.0	0.060	111.14	109.22	1.76
70	6.0	0.060	110.47	109.22	1.15
70	6.0	0.060	108.33	109.22	0.81
70	6.0	0.060	106.13	109.22	2.83

***** TE: Trolox equivalent; DW: Dry weight.

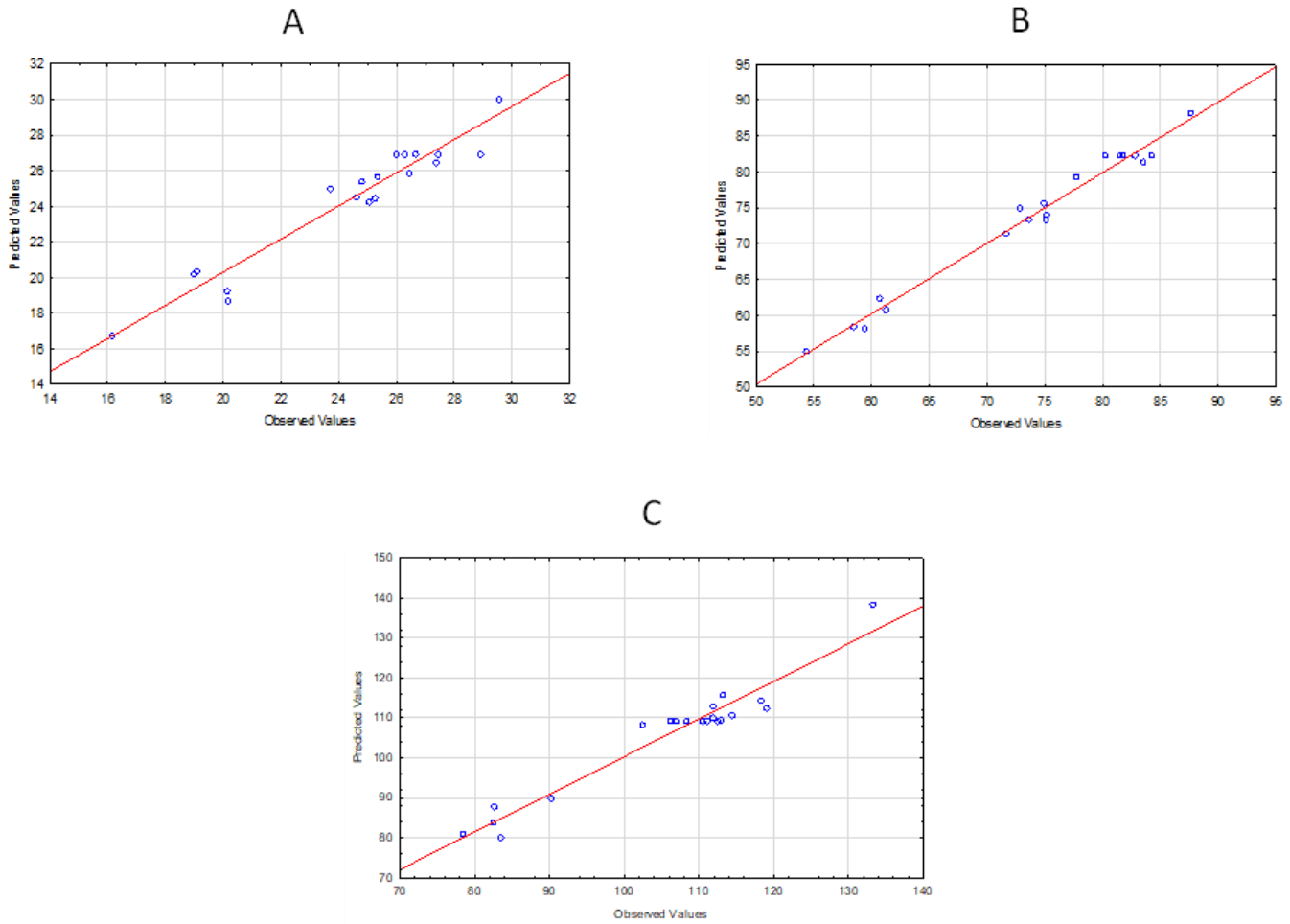

Figure B.2.11. Predict *vs*. observed values of (A) TPC, (B) FRAP and (C) ABTS for the extracts obtained by MAE from the factorial planning.

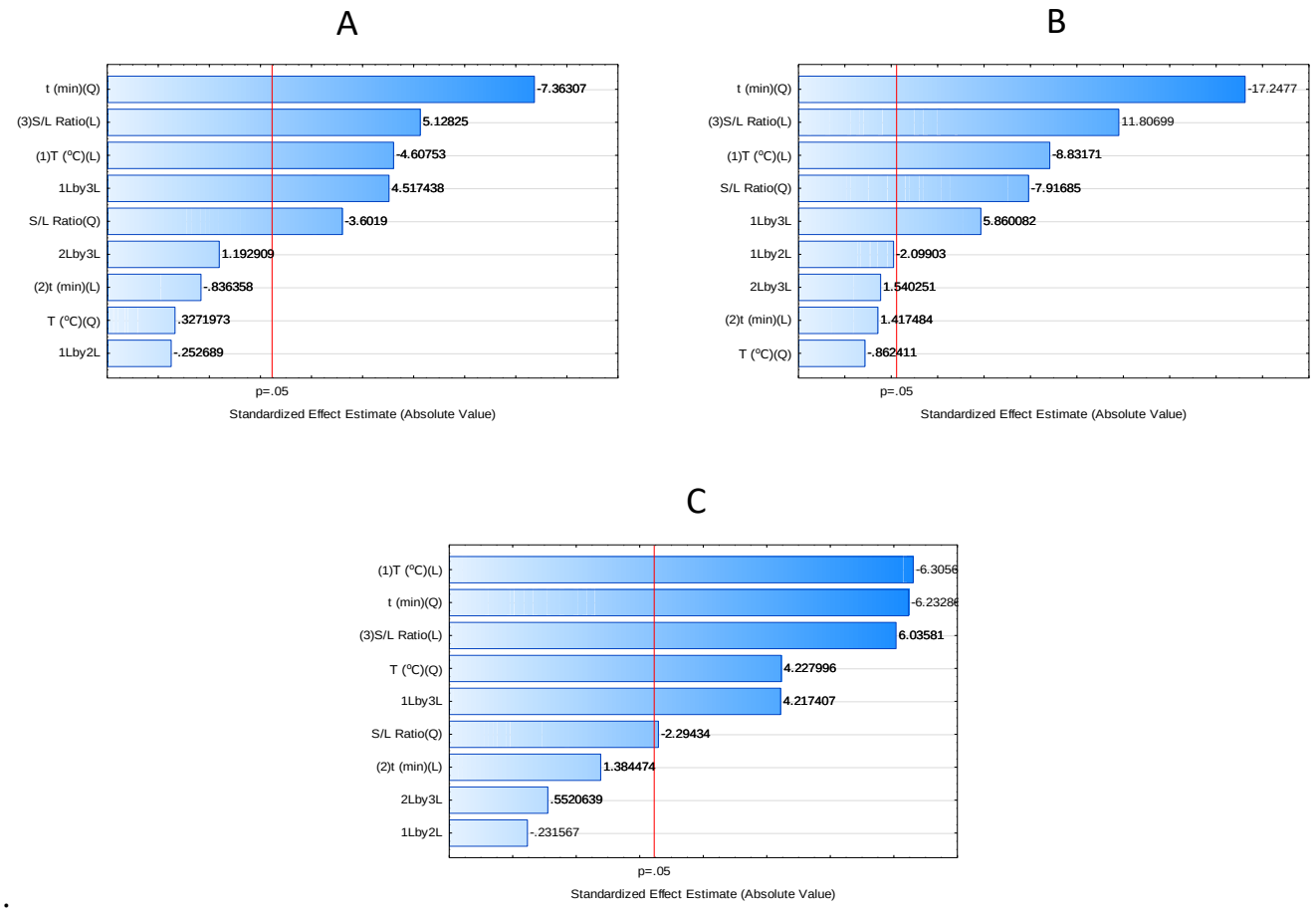

Figure B.2.12. Pareto charts for the standardized main effects in the factorial plannings for (A) TPC, (B) FRAP and (C) ABTS, for the extracts obtained by MAE. The vertical line indicates the statistical significance of the effects (95% of confidence).

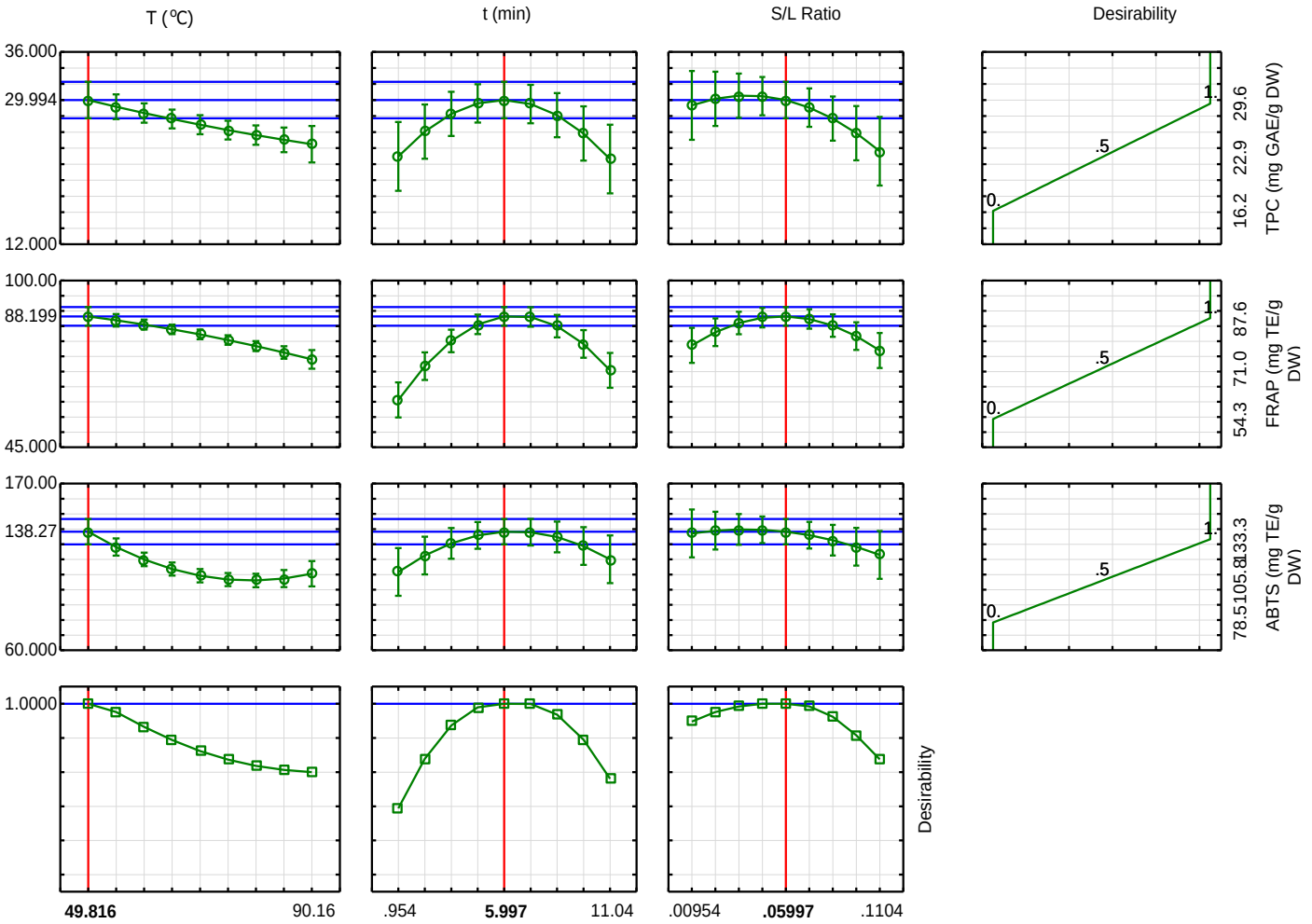

Figure B.2.13. Profiles for predicted values and desirability function for the TPC, FRAP and ABTS for the extracts obtained by MAE from the factorial planning. Red lines indicate optimized values for each variable.

Main phenolic compounds in MAE extracts

Table B.2.16. UHPLC-DAD-MSn data of compounds identified in kiwi peels extracts.

Peak	Rt (min)	Λmax (nm)	$[M-H]^-$ (*m/z*)	MS^n (*m/z*)	Identification
1	6.29	322	297		Caffeic acid derivative
2	7.13	313	341		Caffeic acid hexoside
3	8.40	280	865	739(100),713(60), 577(40), 425(35)	B-type (epi)catechin trimer
4	8.48	280	577	559 (30), 533 (10)451(65),425(100),407(20),289(10)	B-type (epi)catechin dimer
5	8.69	335	369	207(100), 191(40)	Dimethyl caffeic acid hexoside
6	8.80	280	1153		B-type (epi)catechin tetramer
7	9.03	280	289	245(100), 205(20), 203(20), 161(40)	(Epi)catechin
8	9.12	281	1153		B-type (epi)catechin tetramer
9	10.08	280	865	847(95), 821 (30), 739(80),713(75),695(50), 577(100), 575(85), 413(55), 287(20)	B-type (epi)catechin trimer
10	10.53	281	1153		B-type (epi)catechin tetramer
11	10.76	280	865		B-type (epi)catechin trimer
12	11.02	280	865		B-type (epi)catechin trimer
13	11.09	280	461		
14	10.76	280	1441		B-type (epi)catechin pentamer
15	11.41	280, 350	411		Acetyl-dimethyl caffeic acid hexoside
16	12.14	280	609		Quercetin-3-O-rutinoside
17	12.37	280, 350	463	301(1 0 0)	Quercetin-3-O-glucoside

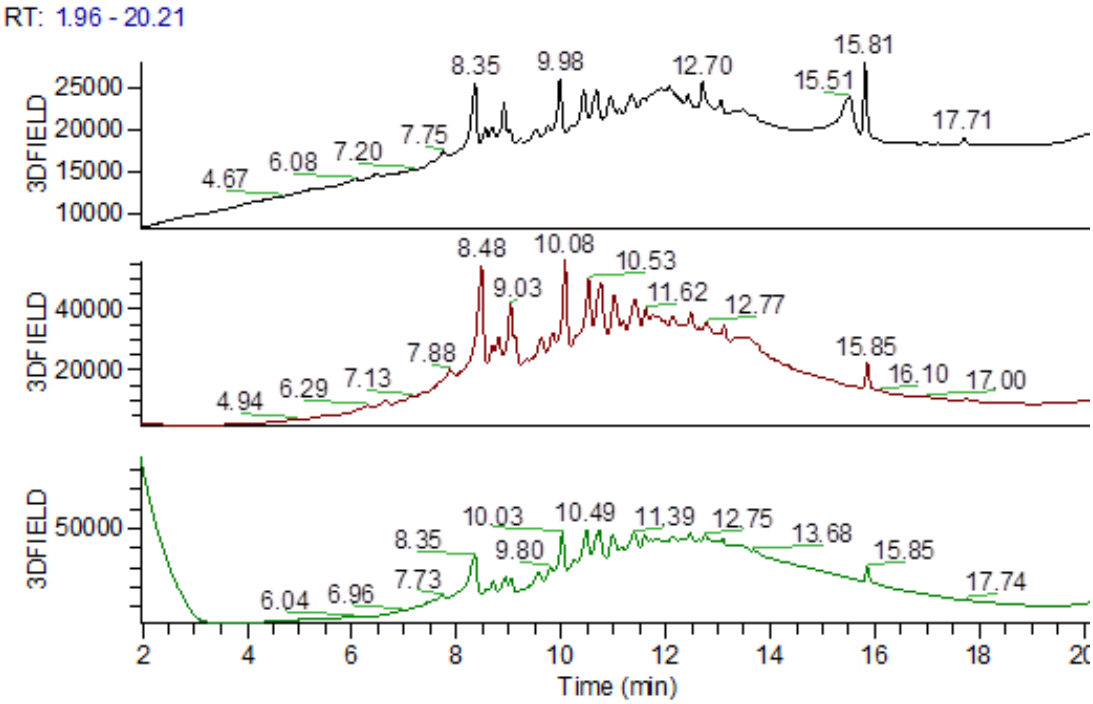

Figure B.2.14. DAD chromatograms of MAE extracts obtained with EtOH: H_2O at 7:3 (wt/wt) (black), acetone (red) and GVL:EtOH at 7:3 (wt/wt) (green).