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REVIEWS

Supercritical CO_2 Extraction and Purification of Compounds with Antioxidant Activity

BEATRIZ DÍAZ-REINOSO, ANDRÉS MOURE, HERMINIA DOMÍNGUEZ,* AND JUAN CARLOS PARAJÓ

Departamento de Enxeñería Química, Facultade de Ciencias de Ourense, Universidade de Vigo, As Lagoas, 32004 Ourense, Spain

Supercritical fluid extraction (SCFE), based on the utilization of a fluid under supercritical conditions, is a technology suitable for extraction and purification of a variety of compounds, particularly those that have low volatility and/or are susceptible to thermal degradation. The interest in SCFE is promoted by legal limitations of conventional solvents for food and pharmaceutical uses. The physicochemical properties of supercritical CO_2 (higher diffusivity, lower viscosity, and lower surface tension than conventional solvents) facilitate mass transfer and allow an environmentally friendly operation. This article presents a comprehensive compilation of data on the supercritical CO_2 extraction of antioxidant compounds from vegetal materials, with particular attention to those of a phenolic nature. Aspects concerning the supercritical operation for extraction and fractionation of antioxidants compounds are considered, including equilibrium solubility of pure compounds and effects of the operational conditions on the antioxidant activity of isolated fractions. The data are compared to those reported for synthetic antioxidants and natural extracts obtained by conventional solvent extraction from vegetal matrices.

Keywords: Activity; antioxidant; SCFE

1. INTRODUCTION

The increasing demand for natural food antioxidants has fostered worldwide research for extracting biologically active substances from a variety of vegetal raw materials. Even though conventional solid−liquid extraction with organic solvents can be used for the same purpose, it may result in the production of nondesirable residues, and the extract can undergo oxidative transformations during solvent removal.

Supercritical fluid extraction (SCFE), supercritical gas extraction, and dense gas extraction are alternative terms to name the operation with a fluid at temperatures and pressures near the critical point. In comparison with conventional, liquid organic solvents, supercritical fluids have a higher diffusivity and lower density, viscosity, and surface tension. On the other hand, the properties of supercritical fluids can be varied over a wide range by changing the operational conditions.

CO_2 (P_c = 7.28 MPa; T_c = 304.1 K) is the most frequently used solvent for SCFE, because of its practical advantages (including its nontoxic and nonflammable character, environmental safety, huge availability, low cost at high purity, and suitability for extracting heat labile, natural compounds with low volatility and polarity). When the extract is recovered in the separators, CO_2 is easily separated because of its high volatility.

SCFE allows the extraction of active ingredients from herbs and plants with a better reproduction of flavor or fragrance than conventional operations. Thermal degradation and decomposition of labile compounds are avoided, due to the operation at reduced temperature, whereas the absence of light and oxygen prevents oxidation reactions. This latter point is of special interest for the extraction of antioxidants, warranting the conservation of their biological properties. Extracts from supercritical treatments with CO_2 (SC-CO_2) can be regarded as all natural, and the products allowed for food applications have the GRAS status. Supercritical fluid-processed materials do not require separate sterilization stages, since Gram-positive and Gram-negative bacteria can be inactivated at mild temperatures. The high-pressure gradient during pressure release can yield extracts free of living microorganisms and their spores, with a longer shelf life than standard solvent extracts (*1*, *2*).

The major disadvantages of SCFE are the high critical pressure, the expensive equipment (*2*, *3*), and the low dielectric constant, which suggests poor solvent power (*4*). The main drawbacks of the process are the high pressure and the associated hazards, which have hindered a wider development. The CO_2 storage tanks and extractors must be properly isolated and equipped with relief systems (*5*).

Supercritical CO_2 behaves as a nonpolar, lipophilic solvent, whose extraction performance is limited by polarity. The use of cosolvents has been proposed as a method to enhance the

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solubility of the target compounds and/or to increase the extraction selectivity, allowing operation at a lower pressure. The decision on whether the use of cosolvents can be regarded as "sustainable" or "green" must be made case by case (*4*).

SC-CO_2 is finding more and more applications as a solvent for extracting valuable compounds from natural products. SCFE is still regarded as a "new" technology since each process requires a new design and is energetically more expensive (*6*) and other extractive technologies are more optimized (*7*). Large capacity plants with optimized design and operation can reduce the costs to the same order of magnitude as those of other proceses, which would be constrained by environmental risks and consumer protection (*2*).

The knowledge of basic information of aspects such as phase behavior of the solutes, mass transfer phenomena, process design, and simulation is necessary to optimize SCFE. Among the economic aspects related to the SCFE, the influence of the plant capacity has been discussed (*3*), and energy, manpower, and cleaning have been identified as the most relevant operating costs. An estimate of the manufacturing cost of SCFE has been reported (*8*−*10*).

SC-CO_2 is particularly suitable for applications in which (i) processing costs are not a limiting factor, (ii) conventional solvent extraction is restricted by environmental regulations, consumer demands, or health considerations, (iii) products have improved quality and/or marketability (for example, when the "natural" character of the product increases the market price), or (iv) traditional processing is not applicable because the product is thermally labile or morphologically unique (*7*). Some of these requirements are fulfilled when the target products must be similar to the natural one, as in the case of flavors, fragrances, food supplements, nutraceuticals, and bioactive principles for cosmetic or pharmaceutical purposes. On the other hand, the manufacture of innovative products (not comparable to those produced by conventional solvent extraction) is a potential application field for this technology (*2, 3*).

A number of review articles and books covering different aspects of SCFE have been published. The state of the art up to the eighties, including a historical perspective, was reported by McHugh and Krukonis (*11*). Fundamentals and modeling of SCFE have been reviewed for chemical processing (*12*) and for food processing (*13*−*16*). Special interest has been paid to pharmaceutical applications, including new developments (*17*), surveys on the broad variety of available processes (*1*), technologies for drug formulation and scale-up (*18*), or analysis (*19*). García-Reverter et al. (*20*) have reported on the industrial trends and history of the main applications.

Critical visions of SCFE for analytical purposes as well as the probable reasons for its declining use (lack of standard procedures, difficulties in extracting polar analytes, and inefficiency in cleanup) have been published by Smith (*21*) and Zougagh et al. (*22*). Other reported studies refer to applications to the analysis of extracts from natural products (*23*) and food samples (*24*), as well as a comparative evaluation with conventional methods (*25*). Chester and Pinkston (*26*) summarized the recent progress in fundamentals, analysis, and novel applications of preparative separations.

In a recent review, Beckman (*4*) focused on CO_2-based systems involving chemical reactions, emphasizing the environmental advantages of this solvent. Aspects related to equipment design, energy requirements, CO_2 release, and recovery have been addressed by Eggers and Sievers (*6*). Extraction of essential oils, flavors, and nonpolar natural products from plants has been reviewed (*27*−*30*), providing information on modeling, simulation, scaling-up, and economic evaluation (*9*). Mukhopadhyay (*31*) and Herrero et al. (*32*) revised different aspects involved in the extraction of natural extracts, with specific attention to natural antioxidants. The current situation and the future trends in industrial SCFE have been concisely summarized by Perrut (*3*). Some data on the extraction of phenolic compounds and vegetable oils with different technologies have been presented recently (*33*). The review of Reverchon (*34*) is a complete approach to analytical, engineering, and modeling aspects of the supercritical extraction of essential oils and related products. The extraction of terpenes from different medicinal plants was revised by Simándi and Kéry (*35*).

SCFE products from plants are complex mixtures of essential oils, esters, terpenes, fatty acids, waxes, resins, and pigments (cited in order of decreasing solubility). Selective SCFE of essential oils can be achieved at 313.2−323.2 K operating below 15 MPa. Some essential oils also contain mono- and sesquiterpenes hydrocarbons, as well as oxygenated mono- and sesquiterpenes with phenolic rings (which are basic structural features for antioxidant activity). Because the total extracts are produced at higher pressures (up to 55 MPa), a part of the available information on the topic covered by this article has been already summarized by Reverchon (*34*). To avoid overlapping with this article, our work will refer to this work when necessary. On the other hand, the extraction of antioxidants such as tocochromanols, lycopene, carotene, and fatty acids from plant and algae (which has been successfully addressed by SCFE) is not covered by the present article.

The aim of the present paper is to review the extraction and fractionation of antioxidants from vegetable materials using CO_2 under supercritical conditions, covering topics such solubility, processing conditions, composition, and properties of extracts, extraction yield, and antioxidant activity of isolates. Particular interest has been devoted to phenolic compounds because of their antioxidant properties.

2. ANTIOXIDANTS

2.1. Antioxidant Activity. The importance of antioxidants in food and in biological systems is well-known. In food systems, the oxidative deterioration of fats and oils results in rancid odors, flavors, and formation of potentially toxic secondary compounds. In the human body, the oxidative damage of DNA, lipids, proteins, and other molecules may contribute to the development of degenerative diseases and cancer. Antioxidants protect foods from oxidation by scavenging free radicals, chelating metals, or acting as singlet oxygen quenchers. In living systems, the antioxidants may raise the levels of endogenous defenses (*36*−*41*).

The diversity of available one-dimensional methods for measuring antioxidant activity for different situations (including type of substrate, operational conditions, initiators, oxidants, oxidation conditions, end points of oxidation, and methods to measure oxidation) makes it difficult to compare and interpret results. For example, the activity with a given test may not be correlated with the results obtained with other tests (*42*). The activity of antioxidants in foods and biological systems depends on the system composition, interfacial phenomena, and partitioning properties of the antioxidants between lipid and aqueous phases (*43*). More realistic information on the antioxidant activity can be achieved by performing different tests for the same problem. The characteristics to be considered for standarizing an assay are presented in the review by Prior et al. (*44*).

A variety of methods for evaluating antioxidant activity are based on the ability to scavenge free radicals, as free radical

generation is directly related to oxidation in foods and biological systems. The radical-trapping methods have been widely used although (i) they lack specificity, (ii) the mechanism of antioxidant protection is not considered, (iii) in complex biological systems partitioning effects and multiple actions can be relevant, and (iv) there is confusion in understanding the significance of results and possible biological implications. The most frequently used radicals are superoxide ($O_2^{\bullet -}$), hydroxyl ($^{\bullet}OH$), nitric oxide ($^{\bullet}NO$), alkylperoxyl ($ROO^{\bullet}$), *N*,*N*-dimethyl-*p*-phenylendiamine ($DMDP^{\bullet +}$), and $DPPH^{\bullet}$ (α,α-diphenyl-β-picrylhydrazyl). The $ABTS^{\bullet +}$ [radical cation of 2, 2′-azinobis(3-ethylbenzothiozoline-6-sulfonate)] is used in the TEAC method (Trolox equivalent antioxidant capacity). Scavenging of hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and peroxynitrite ($ONOO^-$) has also been used. The peroxyl radical plays a key role in autoxidation and can be generated conveniently, as in the TRAP method (total radical-trapping antioxidant parameter, used to determine the antioxidant status of human plasma and expressed as Trolox equivalents) (*45*) or in the ORAC method (oxygen radical absorbance capacity). The reactive oxygen species with relevant biological effects or causing food oxidation were reviewed by Halliwell (*46*) and by Aruoma et al. (*47*), respectively. A method alternative to the usual radical scavenging tests was proposed by Zaporozhets et al. (*48*). Both chelation ability and reducing capacity have been used as indexes of antioxidant activity. The redox potential gives an indication of the effective oxidation/reduction efficiency of all of the antioxidants present in the medium (*49*). The Folin−Ciocalteu test, normally used to quantify phenolic content, has also been used to measure the reducing capacity. The ferric-reducing antioxidant power (FRAP) assay is based on the ability of antioxidants to reduce a ferric complex to the ferrous form (*50*). The degradation rate of the antioxidant substance has been positively correlated with antioxidant activity (*51*). As animal and human models are not suitable for an initial antioxidant screening of antioxidants, the potential of cell culture models for this purpose has been outlined (*52*, *53*). The protective action toward lipid oxidation has been measured for substrates such as pure triacylglycerols, vegetable oils, and lard. Inhibition of oxidation in fish oils and their emulsions is of particular interest, due to their high content in unsaturated fatty acids (highly susceptible to oxidation). Phospholipids and lipoproteins, particularly low-density lipoproteins (*54*), have also been employed as oxidation substrates. Systems involving different phases have been used to offer a realistic approach to the behavior of real systems, among them bulk oil, emulsions, and reverse and aqueous micelles. Liposomes and microsomes have been employed to assess the oxidation in systems resembling practical in vivo conditions, because of the similarity with the lipids making part of biological membranes. Critical reviews on the analytical methods to determine in vitro antioxidant activity of pure phenolics and natural antioxidants have been published (*43*, *44*, *55*−*62*).

2.2. Natural Compounds with Antioxidant Activity. The potential health benefits of phytochemicals found in fruits and vegetables have fostered increasing research on natural products and particularly on those showing antioxidant properties. Many active compounds present in vegetal extracts are of phenolic structure, produced as a natural defense mechanism against radiation or microbial infections. Haslam (*63*) reviewed both fundamental and practical aspects of polyphenols, including structure, biosynthesis, molecular interactions, and processing-derived effects. Antioxidant activities of simple phenolics, benzoic and cinnamic acids, and benzaldehydes (*64*−*67*) and flavonoids (*68*, *69*) have been evaluated. Peptides and proteins (*70*), Maillard products (*71*), sugars and polyols (*72*), and microbial metabolites (*73*) can show antioxidant activity. Besides phenolic compounds, a variety of potential antioxidants (such as carotenoids, vitamin C, and vitamin E) may appear in SCFE products (a topic not covered in this article).

2.3. Sources of Natural Antioxidants. Several literature reviews are available on the growing research oriented to the identification and isolation of active compounds from a variety of feedstocks. In this field, fruits and vegetables and their processed products have been extensively investigated (*57*, *65*, *74*−*77*). Whole grains (*78*), cereals (*79*), mushrooms (*80*), seashore plants (*81*), and seaweeds (*82*) have also been considered as sources of antioxidants. Antioxidant activity was reported for wines and other alcoholic drinks (*45*). Teas contain potent antioxidants and have been studied worldwide due to their high content of phenolic compounds (*83*, *84*). Potent antioxidants are present in olive oil (*85*) and olive processing wastes (*86*). The antioxidant activity of oils and liphophilic fractions has been studied in relation to their components, such as conjugated linoleic acids (*87*) and phospholipids (*88*, *89*). Essential oils contain compounds with antioxidant activities (such as coumarins, coloring substances, and flavones). Other compounds (for example, terpenes) may cause synergistic effects with antioxidants (*90*). This topic has been revised recently (*91*). The antioxidant activity of a variety of plant-derived products has been reported, including smoke flavorings containing lignin dimers (*92*) and effluents from lignocellulosics processing (*93*). Spices, aromatic and medicinal plants, and herbs contain active principles with antioxidant activities (*94*) that have physiological effects in humans (antimutagenic, antiviral, antimicrobial, and antiinflamatory activities). The solid and liquid wastes from processing of agricultural or industrial feedstocks (for example, wine, tea, potato, olive oil, and fish or meat protein) are particularlly attractive as sources of antioxidants. For example, solid wastes containing the hulls, pomaces, and external and fibrous parts of the plants (where the compounds with protective mission and antioxidant activity in the plant are located) can be of special interest (*95*).

3. SOLUBILITY OF MODEL ANTIOXIDANT COMPOUNDS

High-pressure phase equilibrium data under supercritical conditions provide basic information for assessing the separation process and the design of equipment. There are difficulties associated with the determination of equilibrium data, mainly related to the lack of understanding of the dense fluid state, leading to serious uncertainities when the available models are used for calculations near critical points because of the large differences in interactions between the small molecules of the solvent and the large solute molecules (*96*−*98*). Usually, the research works deal with the solubility of a unique solute in a given supercritical solvent, but the presence of other solutes may increase the equilibrium concentration. In this case, the increase in solubility respect to the binary system is related to the solubility of the additional solute, a similar effect to that caused by an entrainer, modifier, or cosolvent during extraction (*99*, *100*), which can be predicted as a function of the physical properties of the pure components (*101*). For example, the presence of the orto isomer of hydroxybenzoic acid (HBA) significantly enhances the solubility of *m*- and *p*-HBA (*102*), the para isomer being less soluble than the ortho or meta isomers (*103*). The solubility of solid mixtures of phenolic compounds in supercritical CO_2 has been studied (*104*, *105*) and summarized by Lucien and Foster (*100*, *106*).

The solubility of solids varies exponentially with the density of the supercritical solvent; the density, the dielectric constant, and the solvating power of SC-CO_2 depend on pressure and temperature. Temperature also influences the solute vapor pressure and the intermolecular interactions in fluid phase. The selectivity of the solvent is affected by the operational conditions, allowing both extraction and fractionation to be performed in a single step. As pressure is increased, the carbon dioxide density increases and the intermolecular mean distance of carbon dioxide molecules decreases, leading to an enhanced specific interaction between solute and solvent molecules. Empirical and semiempirical models do not require the knowledge of physicochemical properties, correlating the solubility of a given solute just with solvent temperature and/or density (*107*, *108*) and also with pressure (*109*−*111*). The correlation based on response surface methodology (*112*) or the empirical models depending on pressure and temperature (*113*, *114*) avoid the necessity of knowing density along the whole range of operating conditions.

The most widely used equations of state (EOS) for correlation and prediction of thermodynamic properties of pure substances and mixtures (Peng−Robinson, Soave−Redlich−Kwong, group contribution associating and statistical associating fluid theory EOS) are derived from the equation first proposed by van der Waals, which was based on fluid density and fugacity calculations, considering the supercritical phase as a dense gas. It has been reported that EOSs do not perform well in systems asymmetric with respect to size and attractive energy, providing results sensitive to the mixing rules for the interaction energy and size parameters of the solute and solvent molecules. The van der Waals mixing rule has been found ineffective for solubility predictions concerning highly asymmetric systems, and several mixing rules have been proposed (*97*, *115*, *116*); its selection is more important than the equation itself (*96*−*97*). Alternatively, mixtures with high nonideality were treated as a pseudo-binary system, and the Peng−Robinson EOS was successfully used to describe the phase behavior (*117*, *118*).

The comprehensive reviews by Dohrn and Brunner (*119*) and by Christov and Dohrn (*120*) summarized the experimental methods and compiled published data of high-pressure fluid phase equilibria from 1988 to 1999, showing the increasing relevance of CO_2 as a solvent. A recent paper by Fornari et al. (*121*) reviewed the solubility of phenolic compounds in SC-CO_2. The solubility of essential oils has been revised by del Valle et al. (*30*), and Reverchon et al. (*34*) summarized some solubilities of pure compounds frequently found in essential oils. Data on the solubility of terpenes (*122*−*126*) have been further published.

Because of the relevance of phenolic compounds on the antioxidant activity, data for pure phenolic compounds are shown in **Table 1**. Solubility data of phenolic compounds in pure or modified SC-CO_2 are presented, as well as the operational conditions and the empirical or thermodynamic correlations suitable for equilibrium predictions. Scarce data on the solubility equilibrium of complex natural extracts are available. Campos et al. (*127*) reported on the solubility of marigold oleoresin. **Figure 1** shows information on the effect of the modifier concentration on the solubility of pure phenolic compounds.

The study of multicomponent systems represents a more realistic approach to the extraction of valuable compounds from a solid matrix. The solubility of a solute in SC-CO_2 depends on both the thermodynamic solubility and the binding of the solute with the solid matrix. Solubility data cannot be used directly unless the solutes have no affinity with the insoluble matrix, but matrix−solute interactions are often more influential on the whole process than bulk solubility.

4. MASS TRANSFER

The solid−liquid extraction is a heterogeneous, multicomponent operation involving the nonsteady transfer of solutes from a solid to a fluid. Vegetal materials contain many different solutes that can be extracted simultaneously at different rates depending on their location (outer surface, pores, vacuoles, etc.) and partition coefficients. The SC-CO_2 extraction involves the following sequential steps: (i) transport of CO_2 from the bulk solution to the external surface of the particle, (ii) CO_2 penetration and diffusion in the solid matrix, (iii) solubilization of the components, (iv) transport of the solute(s) through the solid matrix, and (v) transport of the solute(s) from the external surface of the solid to the bulk solution (external mass transfer). Extraction rates of solutes from vegetal matrices depend on the external mass transfer, effective solute difussivity in the solid, solute solubility in the supercritical solvent, and solute binding to the solid matrix (*29*).

The limiting step of the whole mass transfer rate may correspond to different stages, a fact to be considered when predicting data. A typical extraction curve shows a first stage of constant extraction rate, where the overall process is limited by the external mass transfer, followed by a stage of decreasing extraction rate controlled by both diffusion in the solid particle and external mass transfer, and a final stage where the rate-limiting step is the internal diffusion. In some cases (for example, in the extraction of essential oils), the equilibrium concentration can be much lower than the solubility of the binary system, due to the solute−matrix interactions (*29*, *128*). When matrix−solute interactions are more important for controlling the process than bulk solubility, SFCE can be modeled as a reversible adsorption/desorption process on the matrix either in well-mixed systems (*129*, *130*) or in packed beds (*131*). When the major mass transfer resistances are within the solid phase, a suitable mathematical model must consider the solute(s) transport throught the solid particles.

As revisions on the mathematical models used to predict the SC-CO_2 extraction of essential oils have been published, among others, by del Valle et al. (*29*), Reverchon (*34*), and Sovová (*132*), this kind of information is not included in this article. The models used to correlate experimental results from SCFE can be classified in (i) empirical models, (ii) models based on Fick's second law of diffusion, and (iii) models based on differential mass balances along the extraction bed.

Reported empirical models use exponential (*133*−*136*) or hyperbolic equations (*137*). Mass transfer models dealing with heat transfer analogy (based on the cooling of a solid with a simple geometry such as sphere or plate) have been employed for interpretating the extraction of essential oils with SC-CO_2 (*138*−*140*).

Concerning the second type of model, internal diffusion has been reported as the mass transfer limiting step during the SC-CO_2 extraction of carnosol and carnosic acid from rosemary leaves (*141*) and lignans from *S. chinensis* (*142*). Some active compounds (gingerols, shogaols) were observed to be preferentially extracted during the second and third extraction periods (mixed and diffusional control, respectively) (*143*), but prolonged extraction times may favor the extraction of undesirable compounds (*136*).

The third type of model is based on mass transfer and equilibrium considerations. A combination of desorption and mass transfer resistance (*144*) and axial dispersion has been

Table 1. Solubility of Selected Phenolic Compounds in Pure or Modified SC-CO_2 and Models Employed To Predict Solubility[a]

phenolic compound	*P* (MPa)/*T* (K)/ modifier (% mol or % w)	solubility mole fraction (*y*)	empirical models and equations of state	ref	antioxidant activity reported by
		aldehydes			
anisaldehyde	5.5–13.7/323–373/–	0.2–14 10^{-3}		*104*	*285*, *286*
protocatechualdehyde	10–50/313–333/–	0.01–4.57 10^{-5}	C, SR, PR	*254*	*287–289*
		phenolic acids and derivatives			
benzoic acid	12–28/318–338/–	3.20–98.3 10^{-4}	PR	*255*	commercial antioxidant
	12–28/308–318/–	1.84–12.6 10^{-3}	PR	*99*	
	12–28/308–318/–	1.84–12.6 10^{-3}	mPR	*256*	
	10.1–36.4/308–343/–	0.12–12.8 10^{-3}	PR	*257*	
	10.1–36.4/308–343/–	0.12–12.8 10^{-3}	SRK, PR, EST	*96*	
	10.1–36.4/308–343/–	0.12–12.8 10^{-3}	PR, GA	*258*	
	12–28/308/–	1.25–3.03 10^{-3}	PR, HSVDW	*101*	
	12–28/308/–	1.25–3.03 10^{-3}	HSVDW	*258*	
	10–33/308/A (3.5)	3.34–6.40 10^{-3}	PR, HSVDW	*101*	
	10–33/308/A (3.5)	3.34–6.40 10^{-3}	SAFT, PRSV	*259*	
	9–35/308/M (3.5)	5.33–11.9 10^{-3}	PR, HSVDW	*101*	
	9–35/308/M (3.5)	5.33–11.9 10^{-3}	PR	*260*	
	9–35/308/M (3.5)	5.33–11.9 10^{-3}	SAFT, PRSV	*259*	
	10–30/328/*n*-O (3.5)	2.90–6.07 10^{-3}	PR, HSVDW	*101*	
	10–30/328/*n*-O (3.5)	2.90–6.07 10^{-3}	SAFT, mPR	*259*	
	12–28/318–338/–	0.30–98.0 10^{-3}	RK, SRK, PR	*261*	
	12–28/318–338/–	0.30–98.0 10^{-3}	PR	*256*	
	10–28/308–328/–	0.30–9.20 10^{-3}	log y = f (P, T)	*112*	
	9–23/318/–	1.44–43.1 10^{-4}	ZE	*262*	
	9–23/318/–	1.44–43.1 10^{-4}	GCA	*121*	
o-hydroxybenzoic acid	20.7–41.4/373/–	2.07–6.99 10^{-3}		*103*	*290–294*
	8.1–20.3/308–328/–	0.07–6.24 10^{-4}	KJ, SR, ZE	*263*	
	8.1–20.3/308–328/–	0.07–6.24 10^{-4}	C, VA, Y, Go, J	*111*	
	8.1–20.3/308–328/–	0.07–6.24 10^{-4}	C, VA, Y, Go, Ga	*264*	
	10.1–20.3/328/–	0.32–5.62 10^{-4}	mPR	*100*	
	10.1–20.3/328/–	0.32–5.62 10^{-4}	C, VA, Y, Go, J	*111*	
	8.11–20.3/308–328/–	0.07–6.24 10^{-4}	KJ, SR, ZE	*263*	
	10–22/318–327/–	1.95–63.73 10^{-5}	ZE	*262*	
	10–22/318–327/–	1.95–63.73 10^{-5}		*121*	
	8.6–20.1/318–328/A (3.5)	0.68–2.52 10^{-3}	Gu	*265*	
	9.6–20.1/318–328/M (3.5)	1.25–5.12 10^{-3}	Gu	*265*	
	9.6–25/313–328/–	0.34–5.83 10^{-4}	PR	*266*	
	9.6–25/313–328/–	0.34–5.83 10^{-4}	C, VA, Y, Go, J	*111*	
	9.8–19.5/318/–	0.73–2.89 10^{-3}	PR	*267*	
m-hydroxybenzoic acid	20.7–41.4/373/–	1.12–7.54 10^{-5}		*103*	
	9.1–20.1/318–328/A (3.5)	1.50–5.47 10^{-5}	Gu	*265*	
	9.1–20.1/318–328/M (3.5)	1.59–3.37 10^{-3}	Gu	*265*	
	10.1–20.3/318/–	0.57–3.37 10^{-5}	mPR	*102*	
p-hydroxybenzoic acid	20.7–41.4/373/–	1.33–7.49 10^{-5}		*103*	
	10.1–20.3/318/–	0.14–3.72 10^{-6}	mPR	*100*	
	10.1–20.3/318/–	0.14–3.72 10^{-6}	C, VA, Y, G, J	*111*	
3,4-dihydroxybenzoic acid	10–50/313–333/–	0.023–25.9 10^{-7}	C, SR, PR	*254*	*291–297*
	10–50/313–333/–	0.023–25.9 10^{-7}	GCA	*121*	
o-methoxybenzoic acid	9.98–24.7/308–328/–	0.89–11.1 10^{-2}	C, SR	*268*	
	9.98–24.7/308–328/–	0.89–11.1 10^{-2}	C, VA, Y, Go, J	*111*	
m-methoxybenzoic acid	9.98–24.7/308–328/–	1.65–17.3 10^{-2}	C, SR	*268*	
	9.98–24.7/308–328/–	1.65–17.3 10^{-2}	C, VA, Y, Go, J	*111*	
p-methoxybenzoic acid	9.98–24.7/308–328/–	2.81–9.06 10^{-2}	C, SR	*268*	
	9.98–24.7/308–328/–	2.81–9.06 10^{-2}	C, VA, Y, Go, J	*111*	
	5.5–15.1/323–373 /–	2.87–137.3 10^{-6}		*104*	
o-methylbenzoic acid	11–24.3/313–333/–	9.02–57.0 10^{-4}	C	*269*	
	11–24.3/313–333/–	9.02–57.0 10^{-4}	PR	*260*	
m-methylbenzoic acid	11–24.3/313–333/–	1.84–53.4 10^{-4}	C	*269*	
	11–24.3/313–333/–	1.84–53.4 10^{-4}	PR	*260*	
p-methylbenzoic acid	11–24.3/313–333/–	0.43–7.02 10^{-4}	C	*269*	
	11–24.3/313–333/–	0.43–7.02 10^{-4}	PR	*260*	
BHA	13–20/313–333/–	1.44–4.6 10^{-2}	PR	*270*	synthetic antioxidant
	13–20/313–333/–	1.44–4.6 10^{-2}	C, VA, Y, Go, J	*111*	
caffeic acid	8.5–50/313–333/–	0.08–4.7 10^{-8}	C, SR, PR	*271*	*290–293*, *295*, *297–304*
carvacrol	0.26–30.84/313–323/–	0.029–1.78	PR, mRK	*122*	*305*, *306*
o-coumaric acid	8.5–25/308–323/–	0.21–35.4 10^{-8}	O	*272*	*291*, *307*, *308*
	8.5–25/308–323/–	0.21	C, VA, Y, Go, J	*111*	
m-coumaric acid	8.5–25/308–323/–	0.16–105.5 10^{-8}	O	*272*	*308*
	8.5–25/308–323/–	0.16–105.5 10^{-8}	C, VA, Y, Go, J	*111*	*291–297*, *299*, *304*, *308–311*
p-coumaric acid	8.5–25/308–323/–	0.52–38.5 10^{-8}	O	*272*	
	8.5–25/308–323/–	0.52–38.5 10^{-8}	C, VA, Y, Go, J	*111*	
	8.5–50/313–333/–	0.03–25.5 10^{-7}	C, SR, PR	*271*	

Table 1 (Continued)

phenolic compound	*P* (MPa)/*T* (K)/ modifier (% mol or % w)	solubility mole fraction (*y*)	empirical models and equations of state	ref	antioxidant activity reported by
		phenolic acids and derivatives			
ferulic acid	10–35/308–338/–	2.19–26.5 10^{-7}	C	*273*	*290*, *292–294*, *296–301*, *309–313*
	12–28/301–333/–	1.55–11.8 10^{-6}		*274*	
	12–28/313–333/ E(0.27–3.35% w)	0.24–7.98 10^{-5}	C, AG, So	*274*	
	8.5–50/313–333/–	0.65–433.2 10^{-7}	C, SR, PR	*271*	
gallic acid	20/313/E (2–10)	0.30–20.4 10^{-7}		*182*	*295*, *296*, *298*, *299*, *304*, *310*, *314–319*
methyl gallate	10–50/313–333/–	0.019–4.24 10^{-6}	C, SR, PR	*254*	synthetic antioxidant
propyl gallate	15–25/313–331/–	5.02–18.7 10^{-6}	PR	*270*	synthetic antioxidant
	15–25/313–331/–	5.02–18.7 10^{-6}	C, VA, Y, Go, J	*111*	
	15–25/313–331/–	5.02–18.7 10^{-6}	PR	*275*	
dodecyl gallate	15–25/313–333/–	3.1–20.7 10^{-6}	PR	*270*	synthetic antioxidant
	15–25/313–333/–	3.1–20.7 10^{-6}	PR	*275*	
	15–25/313–333/–	3.1–20.7 10^{-6}	C, VA, Y, Go, J	*111*	
syringic acid	8.5–50/313–333/–	0.01–127.1 10^{-7}	PR	*276*	*302*, *303*, *320*
thymol	5.7–14/323–343/–	0.51–12.6 10^{-3}		*104*	*306*, *321*
vanillic acid	8.6–25/313–328/–	0.48–23.9 10^{-6}	PR	*266*	*290–294*, *297–299*, *302*, *303*, *309*, *310*, *316–318*
	8.6–25/313–328/–	0.48–23.9 10^{-6}	C, VA, Y, Go, J	*111*	
	8.5–50/313–333/–	9.37–607.1 10^{-7}	PR	*276*	
vanillin	8.00–27.65/313–353/–	0.014–1.29 10^{-2}	PR	*277*	*322*
ethylvanillin	8.1–30.15/313–353/–	0.017–3.46 10^{-2}			
o-vanillin	7.83–30.37/313–353/–	0.051–6.50 10^{-2}			
o-ethylvanillin	10.3–30.20/313–353/–	0.119–5.33 10^{-2}			
		flavonoids and others			
catechin	20/313/E (2–10)	0.97–77.5 10^{-8}	PR, SRK	*182*	*315*
	8–13/313/E (5–30)	0.36–32.06 10^{-4}		*278*	
epicatechin	20/313/E (2–10)	0.79–35.6 10^{-8}	PR, SRK	*182*	*315*, *319*
	8–12/313/E (5–30)	0.51–53.6 10^{-4}		*279*	
flavone	9.1–25.3/308–318/–	0.35–5.61 10^{-4}	ZE	*280*	*323*
	9.1–25.3/308–318/–	0.35–5.61 10^{-4}	ZE	*111*	
3-hydroxyflavone	9.1–25.3/308–318/–	0.79–5.56 10^{-4}	ZE	*280*	*323*
quercetin	8–12/313/E (5–30)	0.22–6.37 10^{-3}	GCA, SRK	*281*	*314*, *324–326*
carnosic acid	20–37/313–373/–	1–90 10^{-9}	GCA	*282*	*327*, *328*
	28–40/313–333/ E (0.7–10)	0.60–53.03 10^{-6}	GCA	*283*	
1-hydroxyxanthone	7.4–35.5/305–348/–	1.49–22.20 10^{-4}	O	*284*	
1,6-dihydroxyxanthone	7.4–35.5/305–348/–	1.31–35.88 10^{-4}	O		
1,5,6-dihydroxyxanthone	7.4–35.5/305–348/–	2.80–16.84 10^{-4}	O		
1-hydroxy-3-methylxanthone	7.4–35.5/305–348/–	1.68–30.22 10^{-4}	O		

[a] Abbreviations used: A, acetone; E, ethanol; M, methanol; *n*-O, *n*-octane; and W, water. Empirical and semiempirical models: C, ref *107*; VA, ref *108*; Y, ref *113*; GA, genetic algorith; Ga, ref *112*; Go, ref *114*; J, refs *111* and *264*; O, ref *110*; So, ref *274*; SR, ref *257*; and ZE, ref *109*. Thermodynamic models: AG, Altunin–Gadetskii; EST, Estévez; GCA, group contribution association; Gu, ref *265*; HSVDW, hard sphere van der Waals; KJ, Kumar and Johnston; PR, Peng Robinson; mPR, modified Peng Robinson; RK, Redlich–Kwong; SRK, Soave–Redlich–Kwong; and SAFT, statistical associating fluid theory.

proposed (*145*, *146*). Natural convection phenomena can affect the mass transfer in upflow at low Reynolds numbers (*147*). The existence of a fraction with different proportion of broken cells has been considered for data interpretation, an approach similar to that used in the extraction of vegetable oil (*132*, *144*, *148*−*150*). Assuming pseudo-steady state, plug flow, and constant temperature, pressure, and solvent velocity, this approach provides a simple analytical solution to the mass balance equations, giving a good interpretation of the extraction of essential oil from black pepper (*151*, *152*), aniseed (*153*), ginger oleoresin (*143*), artemisinin (*137*), and rosemary (*154*).

5. SCFE OF NATURAL SOURCES: EFFECTS OF THE OPERATIONAL CONDITIONS

The knowledge of the effects caused by the operational variables (temperature, pressure, solvent flow rate, solvent-to-feed ratio, modifier type, and concentration and separation conditions) on a given SCFE process is necessary for optimization and process design. Designs of experiments have been applied to optimize the extraction yield of solubles, total phenolics, bioactive compounds, and/or antioxidant activity of extracts (*143*, *155*−*163*). In the next sections, the effects of the most influential variables on SCFE are considered and particularized for the production of antioxidant extracts. As in any extraction process, the type of raw material (cultivar, variety, mechanical, and thermal treatment) has a strong influence, as it has been reported for both the extraction yields and the antioxidant activity of the SC-CO_2 extracts from *Terminalia catappa* leaves (*164*) and wine industry byproducts (*165*) and for the yield of lignans from flowers, leaves, and seeds (*142*).

5.1. Pressure and Temperature. The extraction pressure is an influential parameter on SCFE, since both density and solvent capacity increase with pressure. The conditions employed to extract phenolic antioxidants are usually harsher than those used in the extraction of essential oils: Usually, oils are soluble at pressures lower than 10 MPa and temperaturares in the range of 313.2−328.2 K, whereas increased pressures result in enhanced extraction of polar and high molecular mass com-

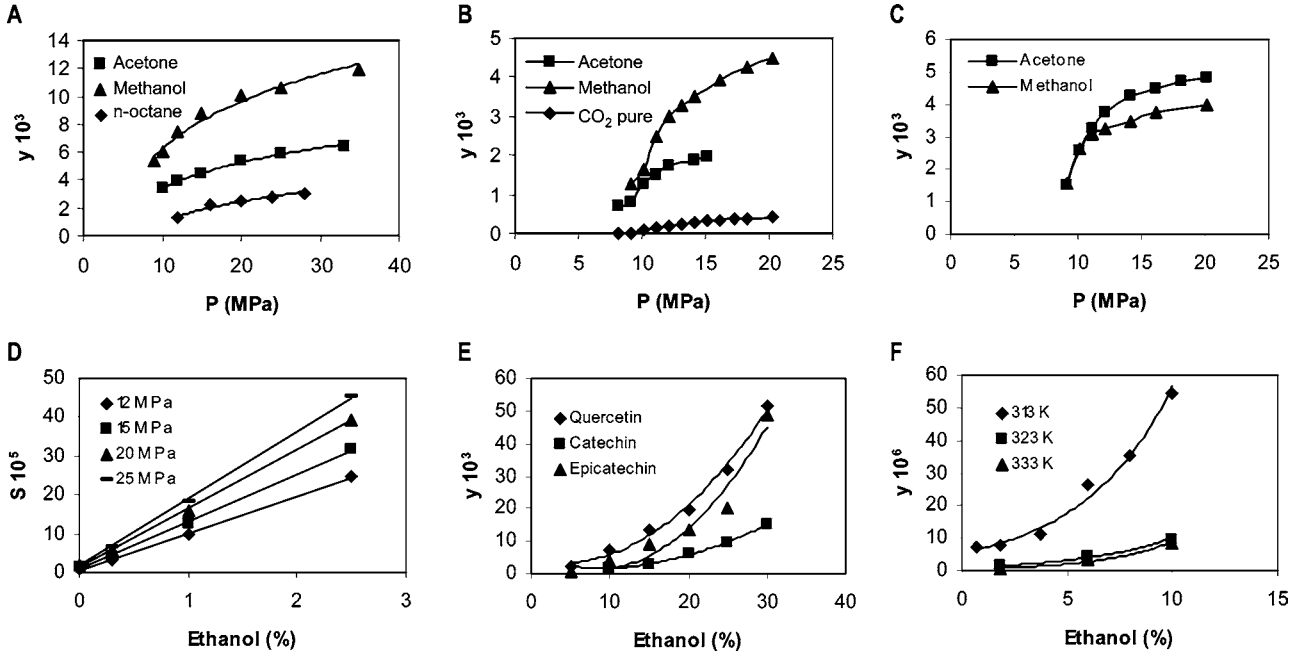

Figure 1. Effect of the presence of modifier on the solubility of (**A**) benzoic acid at 308 K (*101*, *112*); (**B**) *o*-hydroxybenzoic acid at 318 K (*263*) and in the presence of 3.5% mol acetone and 3.5% methanol (*265*); (**C**) *m*-hydroxybenzoic acid at 318 K (*100*) and in the presence of 3.5% mol acetone and 3.5% methanol (*265*); (**D**) ferulic acid (*274*); (**E**) catechin at 313 K (*278*), epicatechin at 313 K (*279*), and quercetin at 313 K (*281*); and (**F**) carnosic acid at 33.5 MPa (*283*).

pounds (including polyphenols, the major antioxidants in plant extracts). When no high molecular weight compounds are present (for example, in savory oil), an increase in extraction pressure does not enhance the extraction yield (*166*).

The use of low pressure (10 MPa) allowed similar extraction yields as liquid CO_2, but an increase from 25 to 35 MPa doubled the extraction yield of essential oils (*167*). Pressures over 50 MPa improved the amount and quality of marigold extracts (*168*). Even though higher pressures or temperatures do not guarantee improvements in extraction in some cases (*169*), in other cases (for example, processing of *Labiatae* herbs), pressures up to 100 MPa have been used to obtain higher yields at faster rates without reduction in the antioxidant activity of the extracts (*170*).

Further increases in extraction pressure beyond a threshold point result in higher fluid viscosity and reduced diffusion coefficients. In operation at high pressure, increased temperatures may lower the extraction yield due to the reduction in density and the solvent power of the fluid. High-temperature SC-CO_2 can provide a higher antioxidant activity than operation at lower temperatures even if the extraction yield could decrease due to the lower SC-CO_2 density. Highly thermal sensitive compounds require mild extraction conditions to avoid alteration (for example, some phenolic compounds can be polymerized or oxidized at temperatures higher than 50 °C), although other phenolics are more resistant (*170*). In some studies, a threshold to avoid thermal degradation has been established (for example, 313.2 K for oregano oleoresin) (*171*). The SC-CO_2 of phenolic diterpene antioxidants from rosemary provides enhanced extraction yields of carnosic acid and carnosol at the highest component ratio, since carnosol is produced by oxidation of carnosic acid (*141*, *172*). SC-CO_2 extraction minimizes the thermal decarboxylation of the anacardic acids from cashew nut shell (*173*) and improves extraction yield of hyperforin from *Hypericum perforatum* (*174*), carnosol from marjoram (*175*), antioxidants from aloe (*162*), and matricine from chamomile (*169*). The matricine degradation on SCFE reported by Kaiser et al. (*176*) was due to (i) the coextraction of water, which accelerates the hydrolytic cleavage, and (ii) the high extraction temperature used (333.2 K). Color and texture of bamboo extracts were influenced by the extraction temperature, which can also be selective to some compounds (*177*). The extraction temperature has a different effect on the solubility of some antioxidants depending on the operating pressure (*178*).

5.2. Modifier. SC-CO_2 is suitable for extracting oils and lipophilic compounds, but many natural products with biological activity (including natural phenolic antioxidants) are poorly soluble in this solvent. Modifications in pressure and temperature could cause limited effects on the extraction of substances such as flavonoids and terpenoids. The utilization of pure CO_2 as a solvent for SCFE may result in poor extraction yield and purity, as it has been reported for the extraction of bioactive compounds from boldine (*179*, *180*).

Separation can be enhanced by using a modifier able to interact with the target compounds. As SCFE is affected by polar forces, the limited polarizability of CO_2 (26.5×10^{-25} cm^3) limits the solubilities of solid aromatic compounds, which are several orders or magnitude lower than in a conventional liquid solvent. The addition of small amounts of a hydrogen bond acceptor or Lewis base cosolvent results in large solubility enhancements (*101*). The presence of modifiers increases the interaction of solutes with the solvent by increasing density, allowing specific chemical interactions (for example, hydrogen bonding) and possibly by altering the structure of the vegetal matrix (causing swelling, structural changes), and/or by breaking polar interactions of the solute and the matrix (*181*). The use of a suitable cosolvent may improve the performance and the economic feasibility of a given process, improving the extraction yield and separation selectivity even in operation at a lower pressure with a reduced recycling ratio.

In some cases, as in the extraction of aloe antioxidants, the modifier has little or no effect on the yield (*162*) or extraction rate but improves the extract composition with respect to bioactive compounds, as in the extraction of gingerols and

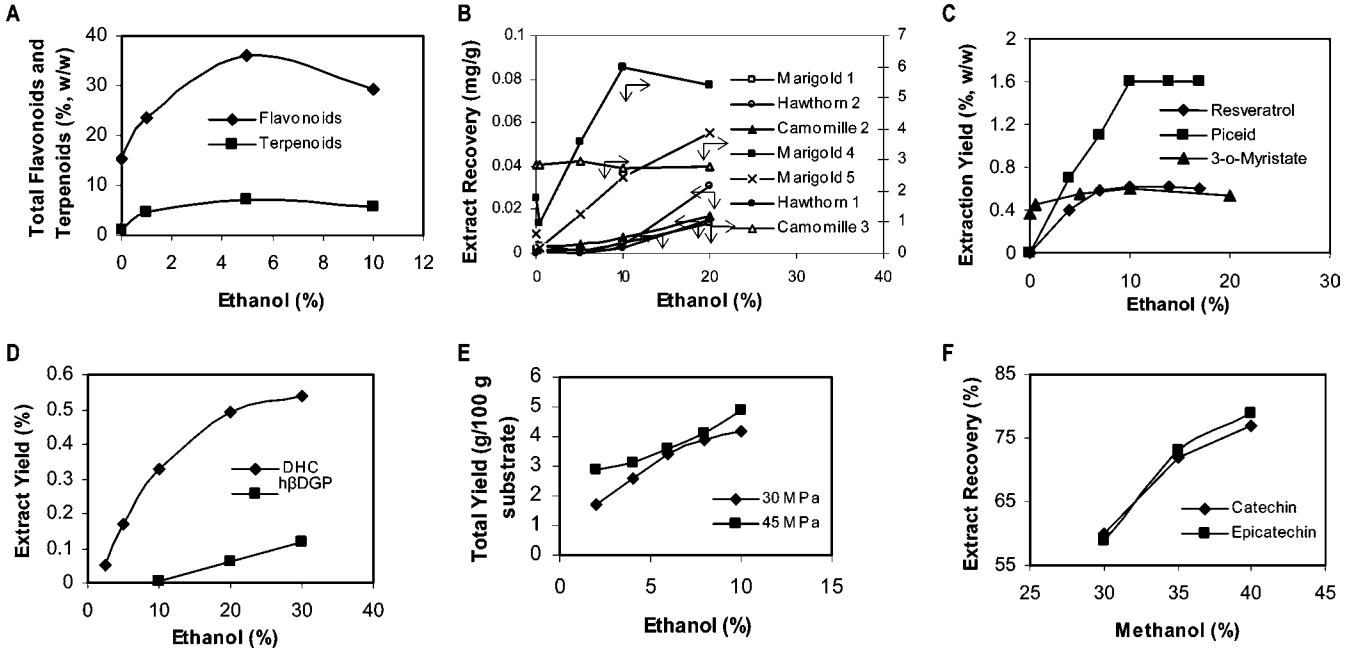

Figure 2. Effect of the cosolvent (ethanol) concentration on the SC-CO_2 extraction and recovery yield of antioxidants from plant materials in the extraction of (**A**) total flavonoids and terpenoids from *Ginkgo biloba* (*157*); (**B**) isorhamnetin-3-*o*-(2″,6″-dirhamnosyl)glucoside, faradiol-3-o-myristate, and faradiol-3-*o*-palmitate from marigold, epigallocatechin gallate and vitexin-2″-*o*-rhamnoside from hawthorn and luteolin, and matricaria spiroketal from chamomille at 323 K and 30 MPa (*181*); (**C**) resveratrol and piceid from *P. cuspidatum* at 323 K and 30 MPa (*388*) and faradiol-3-*o*-myristate at 323 K and 50 MPa (*168*); (**D**) the yield of 5,8-dihydroxycoumarin (DHC) and 5-hydroxy-8-O-β-D-glucopyranosylbenzo-pyranone (hβDGP) from *Hierochloë odorata* at 35 MPa and 313 K (*203*); and (**E**) the extract yield from boldo at 45 MPa and 323 K (*381*). (**F**) Results achieved with methanol as a cosolvent during extraction of catechin and epicatechin extracted in 1 h at 67.8 MPa and 353 K from deoiled grape seed (*236*).

shogaols from ginger (*143*). The use of increasing amounts of modifier allows extraction of, first, the low polar and then the more polar compounds. A progressive increase in pressure and modifier proportion allows the extraction of phenols with increasing molecular weight, as reported for the processing of grape seed concentrates (*182*). Used as a modifier, ethanol enhances the SC-CO_2 extraction of phenols: Just low molecular weight phenols can be extracted with 2% ethanol, catechin and epicatechin can be separated with 5% ethanol, epicatechin gallate can be extracted with 10% ethanol, and proanthocyanin dimers can be recoved with 15% ethanol. Higher ethanol proportions also improve the yields of low molecular weight phenols.

The utilization of two modifiers has been proposed for defined situations. Methanol and citric acid have been proposed as modifiers to improve the extraction of polyphenolics from grape seed extract for analytical purposes (*183*). Mixtures of methanol:water have been reported to be the best modifier to extract flavonoids from *S. radix* (*184*), and mixtures of ethanol:isopropyl alcohol have been proposed for obtaining turmeric extracts (*185*, *186*). Methanol containing 0.2% formic acid enhanced the recovery of rosmarinic acid from Lemon balm, but the results were not comparable to those obtained with conventional solvent extraction (*187*).

The common modifiers used in SC-CO_2 extraction were as follows:

Alcohols. The most frequently used are methanol and ethanol, which show ability for inducing dipole/dipole interactions and hydrogen bonding with polar functional groups. The use of methanol as a modifier requires a slightly higher temperature (335.7 K) to reach the supercritical state (*188*). Increased methanol concentrations may improve the extraction yields, but the temperature necessary to reach the supercritical state is higher (346.6 K for systems containing 15% methanol) and could be not suitable for natural products. In the extraction of antioxidants from tamarind seed coat, the utilization of methanol as a modifier increased yields over operation with pure CO_2, but they were still lower than the ones obtained with ethyl acetate extraction (*189*). Ethanol has been employed as a cosolvent to increase the solubility of ginseng oil and ginsenoids (*190*), polyphenols from plants (*191*), antioxidants from *Eucalyptus* (*192*), and olive leaves (*193*). Ethanol favored the extraction of lipophilic, nonvolatile compounds from marigold, showing the same effect as an increase in the extracting pressure, and improved the yield of lipophilic compounds as 3-*O*-myristate, the active compounds in marigold extracts (*168*). The experimental conditions can influence the color of the extracts (*157*), and for a given temperature, the presence of modifier facilitates the extraction of colored substances or undesirable compounds, such as chlorophyll, when using ethanol (*194*). Ethanol significantly enhanced the extraction of flavonoids and terpenoids from *G. biloba*, and high ethanol proportions (in the range of 5−10%) resulted in a reduction in the purity of the active compounds due to coextraction of other undesired compounds (*157*).

Lignans, optically active dimers of phenylpropanoids, can be extracted between 20 and 40 MPa and 310 and 353 K with 10% ethanol or 5−20% methanol as cosolvents (*195*, *196*). Both cosolvents did not alter the proportion of compounds in extracts from *P. edulis* with respect to operation with conventional solvents, showing similar chromatographic profiles (*197*). Methanol was used as a modifier for the extraction of magnolol (*198*), soy isoflavones (*199*), flavonoids from chamomille (*169*, *176*), or from *Passiflora* (*197*), phenolics from grape seed (*182*), pistachio hulls (*160*), or aloe extracts (*162*), whereas 2-propanol was used for the extraction of ginger oleoresin (*143*). **Figure 2**

Table 2. Extraction of Phenolic Compounds with Antioxidant Activity from Plant Materials by SC-CO_2 and Conventional Solvent Extraction[a]

vegetal material (Latin name)	CO_2 SCFE conditions[b] *P*/*T*/mod/time/flow rate // S_i (P_i/T_i)	extraction yield (total extract, TE, and active compounds) (conventional solvent)[c]	antioxidant activity[d]	ref
aloe vera leaf skin (*Aloe barbadensis* Miller)	45/305/E (10)/–/36 // S_1 and S_2 (–/313) 40/314/–/–/36 // S_1 and S_2 (–/313) 35/323/E (20)/–/36 // S_1 and S_2 (–/313)	flavonoids = 0.13 flavonoids = 0.46 flavonoids = 1.50	IP_{DPPH} = 33.5% IP_{DPPH} = 10.7% IP_{DPPH} = 10.3% $IP_{DPPH,Trolox}$= 76.8% $IP_{DPPH,BHT}$ = 35.9%	*162*
baical skullcap root (*Scutellaria baicalensis*)	20/313/–/0.5/– // S (5/298) AC[e] 20/313/–/0.5/– // S (5/298) Se[e]	flavonoids = 0.27	IP_{DPPH} = 14.22–14.84% IP_{DPPH} = 16.20–17.01%	*230*
baical skullcap root (*S. baicalensis*)	20–40/313–343/M (4.7–13)/0.75/– 20/323/M:W (7:3) (13)/0.75/– 20/323/M (13)/0.75/– Me:W (70:30)	CE = 6.4–19.91 flavonoids: Ba (13.8); Bae (0.86); W (0.22) flavonoids: Ba (2.56); Bae (0.48); W (0.37) CE_M = 16.02; CE_E = 16.12; CE_{EA} = 3.13 flavonoids: Ba (11.3); Bae (0.57); W (0.23)	*329*	*184*
boldo (*Peumus boldus* M.)	40/313/–/2.5/1.5 kg/h 60/333/–/2.5/1.5 kg/h	TE = 1.6; B (0.0013) TE = 2.9; B (0.0031) TE_{WE} = 12–34; B (0.06–0.12)	$TEAC_{1g}$ = 0.006 $TEAC_{1g}$ = 0.008	*179*
boldo (*P. boldus* M.)	9/313/–/3/1.5 kg/h 60/333/–/3/1.5 kg/h 45/333/E (5)/3/1.5 kg/h	TE = 2.8%; B (n.d. mg/kg) TE = 5.1%; B (2.3 mg/kg) TE = 4.9%; B (7.4 mg/kg) TE_M = 36.6%; B_M (59.7 mg/kg)	AP = 5.0 L/mg AP = 14.9 L/mg AP = 17.1 L/mg AP_M = 69.2 L/mg	*381*
bushy lippia (*Lippia alba*)	40/333/–/2/–	MTpH (24.6); MTpn (43.7); OMTp (1); STpH (29.4); OSTp (1.1)[g] HD: MTpH (33.3); MTpn (54.0); OMTp (0.8); STpH (11.3); OSTp (0.9)[g]	*330*, *331*	*330*
bushy lippia (*L. alba*)	8/313/–/5/– 12/313/–/5/– 12/323/–/5/– 10/318/–/5/–	TE = 4.1; Lm (15.3); Cv (50.2) TE = 5.6; Lm (2.0); Cv (64.0) TE = 2.2; Lm (17.0); Cv (53.0) TE = 7.0; Lm (0.5); Cv (32.1) TE_E = 21; TE_{HD} = 0.8; Lm (24); Cv (13.4)		*126*
cashew nut shell (*Anacardium occidentale* L.)	25/313/–/17.5/4–5 kg/h	TE = 18.7 (Ana, Cds, Cdn)	*332*, *333*	*382*
cashew nut shell (*A. occidentale* L.)	30/333/–/2/180 14.7/313/–/1/180 29.4/333/–/4+4[f]/300 29.4/333/–/1+5[f]/300 9.8+29.4[f]/333/–/1+4[f]/ 300	TE = 4.0 (Ana, Cds) TE = 1.2 (Ana, Cds) TE = 15.8 (Ana, Cds) TE = 15.9 (Ana, Cds) TE = 14.4 (Ana, Cds)		*173*
chamomile (*Matricaria chamomilla*)	20/313/–/0.5/60 20/ 318/M (5)/0.5/0.6 20/ 313/–/2/0.6 (pilot plant) // S_1 (20/273), S_2 (0.8/333)	Apg (71.4)/Apg-7-g (0.8)[h] Apg (143.3)/Apg-7-g (14.6)[h] Apg (56.1)/Apg-7-g (0.5)[h]	*334*, *335*	*169*
chamomile (*Matricaria recutita*)	50/323/E (5)/–/0.6 69/323/E (20)/–/0.6	HP (0.002)/L (0.007)/*M*SPK (3.19) mg/g HP (0.017)/L (0.032)/*M*SPK (4.36) mg/g	*336*	*181*
chamomile (*Chamomilla recutita*)	10/303/–/10/0.24 kg/h // S (–/273) 10/313/–/10/0.24 kg/h // S (–/273) 20/303/–/10/0.24 kg/h // S (–/273) 20/313/–/10/0.24 kg/h // S (–/273)	TE = 3.25% TE = 1.95%; α-B/Ch (20.89)[g] TE = 3.90% TE = 4.35%		*228*
chamomile (*C. recutita*)	pilot scale (three stages) 1) 38/333/M (23)/3/– 2) 38/333/ M (23)/3/– 3) 10/343/M (24)/3/– // S (4/281) 9/313/–/3/8 kg/h // S (4/281) 10/343/M (28)/3/– // S (4/281)	1) TE = 7.24; Apg-7-g (4.66) mg/g 2) TE = 2.29; Apg-7-g (19.5) mg/g 3) TE = 9.65, Apg-7-g (43.2) mg/g Apg (20.9–33.4)/Apg-7-g (n.d.) mg/g TE = 16.3%; Apg-7-g (21.9) mg/g		*176*
coriander seeds (*Coriandrum sativum*)	oil: 10/313/–/–/– 17.7/321/–/0.25–1/0.08 kg/h 18.8/331/–/0.25–1/0.09 kg/h	TE = 1.849 TE = 1.918	$IP_{DPPH,eugenol}$ = 95.8% IP_{DPPH} = 55.7% IP_{DPPH} = 57.4%	*158*
echinacea (*Echinacea purpurea*)	20/313/–/–/6 kg CO_2/kg herb 30/313/–/–/6 kg CO_2/kg herb 30/323/–/–/6 kg CO_2/kg herb	TE = 0.72 TE = 1.25 TE = 1.60	*337*, *338*	*383*
eucalyptus leaves (*Eucalyptus camaldulensis* var. *brevirostris*)	40/343/E (10)/2/0.12 40/343/E (15)/2/0.12	TE = 12.0 TE = 16.6 TE_E = 14.0–20.0	OI_{FTC} = 61% OI_{FTC} = 73% $OI_{FTC,E}$ = 70–82% $OI_{FTC,BHA}$= 64% $OI_{FTC,BHT}$ = 81%	*192*
eucalyptus leaves oil (*E. camaldulensis* var. *brevirostris*)	20/323/–/2/0.12	MTpH (0.242%); STp (0.0825%) pCl (1.16); oHC (0.17); MEP (0.34); Thy (0.98)[g] HD: pCl (0.58); oHC (0.18); Thy (0.65)[g]	OI_{FTC} = 59% OI_{FTC} = 50%	*233*
fennel seeds (*Foeniculum vulgare*)	8/313/–/4/0.2 kg/h // S (1.4/ 298) 10/313/–/4/0.2 kg/h // S (1.4/ 298) 15/313/–/4/0.2 kg/h // S (1.4/ 298)	TE = 2.4; MTpH (1.65; 90); *t*-A (72.8); BDADOE (0.17) TE = 3.9; MTpH (2.00; 92); *t*-A (73.3); BDADOE (0.35) TE = 5.2; MTpH (2.55; 85); *t*-A (68.6); BDADOE (0.66)	*339*, *340*	*212*
fennel seeds (*F. vulgare*)	9/313/–/3/2.3 kg/h // S_1 (8/263), S_2 (2/263)	TE = 3.2		*384*

Table 2 (Continued)

vegetal material (Latin name)	CO_2 SCFE conditions[b] *P*/*T*/mod/time/flow rate // S_i (P_i/T_i)	extraction yield (total extract, TE, and active compounds) (conventional solvent)[c]	antioxidant activity[d]	ref
ginger	10/313/–/5–5.25/0.09 kg/h		$IO_{\beta c-LA,3h}$ = 44%	*186*
(*Zingiber officinale*)	30/303/–/5.75–6/0.065 kg/h		$IO_{\beta c-LA,3h}$ = 43%	
ginger	20/313/–/1/0.20 kg/h	MTp = 3.6; STp = 37.9; HC = 35.1		*385*
(*Z. officinale*)	20/313/–/2/0.20 kg/h	MTp = 5.2; STp = 37.6; HC = 40.2		
	25/313/–/1/0.20 kg/h	MTp = 3.5; STp = 35.0; HC = 39.1		
	25/313/–/2/0.20 kg/h	MTp = 4.1; STp = 38.6; HC = 37.4		
ginger	20/318/–/–/–	TE = 4.6; Zg (1.6); Ggl (10.1)		*31*
(*Z. officinale*)		TE_H = 4.9; Zg (31.6); Ggl (5.4)		
ginger	20/308/–/–/0.21 kg/h	TE = 2.65; OMTp (9.2); STp (40.1); Ggl; Shl (50.7)[g]	$AA_{\beta-c}$ = 83%; $AA_{\beta-c,control}$ = 45%	*143*
(*Z. officinale*)	20/298/E (1.17, % w)/–/0.16 kg CO_2/h	TE = 2.31; OMTp (8.5); STp (45.2); Ggl; Shl (46.2)[g]		
	20/298/iP (1.17, % w)/–/0.16 kg CO_2/h	TE = 2.14; OMTp (9.6); STp (45.0); Ggl; Shl (45.4)[g]	$AA_{\beta-c}$ = 85%; $AA_{\beta-c,control}$ = 60%	
	20/308/E (1.17, % w)/–/0.15 kg CO_2/h	TE = 2.48; OMTp (8.8); STp (41.7); Ggl;Shl (49.4)[g]		
	25/308/iP (1.17, % w)/–/0.19 kg CO_2/h	TE = 2.19; OMTp (9.3); STp (48.4); Ggl; Shl (42.3)[g]		
ginseng root hair	31/308/–/4/–	$TE_{ginsenosids}$ = 73 mg/kg adsorbent	*341*	*190*
(*Panax ginseng*)	31/333/–/4/–	$TE_{ginsenosids}$ = 108 mg/kg adsorbent		
	31/333/preloaded E (2.7)/4/–	$TE_{ginsenosids}$ = 91 mg/kg adsorbent		
	31/308/preloaded E (6)/4/–	$TE_{ginsenosids}$ = 800 mg/kg adsorbent		
	31/333/preloaded E (6)/4/–	$TE_{ginsenosids}$ = 1141 mg/kg adsorbent		
		$TE_{E,ginsenosids}$ = 2028 mg/kg adsorbent		
grape marc	35/323/M (5)/0.25/0.24	flavonols (Res, C, EC)	*342–344*	*249*
(*Vitis vinifera*)		phenolic acids (SlA, GeA, SA, SnpA)		
grape seed	oil: 45.4/308.2/–/0.25/–		*315*, *344–347*	*237*
(*V. vinifera*)	45.4/308.2/M (5:1)/0.25/–	GA/C/EC		
grape seed	20/313/M (5)/–/30	GA (0.05); PCA (0.12); PCAD (0.20)		*182*
(*V. vinifera*)	20/313/M (15)/–/30	GA (2.43); PCA (0.75); MGG (0.04); PCAD (0.22); C (0.21); EC (0.05)		
	30/313/M (5)/–/30	GA (0.21); PCA (0.12); PCAD (0.21)		
	30/313/M (15)/–/30	GA (2.71); PCA (0.77); MGG (0.08); PCAD (0.24); C (0.33); EC (0.05)		
grape seed	oil: 65.4/353/–/1/0.12 // S (–/298)			*236*
(*V. vinifera*)	65.4/353/M (30)/1/0.12 // S (–/298)	C (60)/EC (59)		
	65.4/353/M (35)/1/0.12 // S (–/298)	C (72)/EC (73)		
	65.4/353/M (40)/1/0.12 // S (–/298)	C (77)/EC (79)		
grape skin	15/313/E (7.5)/0.75/0.12	Res (35.6–170.6 mg/kg)	*315*, *347*, *348*	*386*
(*V. vinifera*)				
grapefruit peel	9.5/323/E (10)/0.25/–	Nar (1.08, wet basis)	*349*, *350*	*188*
(*Citrus paradisi* L.)	9.5/332/E (15)/0.75/–	Nar (1.44, wet basis)		
	9.5/336/M (10)/0.25/–	Nar (0.92, wet basis)		
		E: Nar (1.52, wet basis)		
guaco leaves	10.1/343/–/0.5/–	TE = 0.5%; Cmr (0.4 mg/g)	*351*	*210*
(*Mikania glomerata*)		TE_H = 0.67%; Cmr (0–5.2 mg/g)		
hawthorn	50/323/E (20)/–/0.036	EGCG (1.410)/V2OR (0.034)/ GCG (0.635) mg/g	*277*, *352*, *353*	*181*
(*Crataegus* sp.)	69/323/E (20)/–/0.036	EGCG (2.680)/V2OR (0.064)/ GCG (0.832) mg/g		
helichrysum dried flower heads	26/323/–/3/50 kg/h	flavonoids: TE = 4.5–4.9	$SO_{100\mu g/mL}$ = 40.3–100	*211*
(*Helichrysum italicum*)	commercial	TE = 3.9	$SO_{SOD,500U/mL}$ = 100	
			$SO_{com,75\mu g/mL}$ = 100	
			$IP_{DPPH,100\mu g/mL}$ = 74–95%	
			$IP_{DPPH,BHA15\mu g/mL}$ = 92%	
			$IP_{DPPH,comml,100\mu g/mL}$ = 94%	
			$RAA_{\beta-c}$ = 0.57–0.71	
			$RAA_{\beta-c,BHA}$ = 1	
			$RAA_{\beta-commercial}$ = 0.78	
hiprose	30/318/–/1/–	TE = 0.63	354	*191*
(*Rosa majalis* L.)				
hop	commercial	total phenols (0.52–3.79)/ total flavanoids (0.2–0.92)	$T_{inh\ inc}$ = 2.2 min	*387*
(*Humulus lupulus*)				
hop	12–28/313–333/–/4/1.2 kg/h // S (–/45–60)	TE = 3.3–16.6		*159*
(*H. lupulus*)				
hu zhang roots	30/323/ E (1.7)/2/20 kg/h // S (5/213)	TE = 12.5; Res (5.17%)[i]; Pc (13.0%)[i]	*355*	*388*
(*Polygonum cuspidatum*)	15/323/ E (1.0)/2/20 kg/h // S (5/213)	TE = 8.2; Res (7.21%)[i]; Pc (2.46%)[i]		
	20/323/ E (1.0)/2/20 kg/h // S (5/213)	TE = 9.6; Res (6.81%)[i]; Pc (9.41%)[i]		
	25/323/ E (1.7)/2/20 kg/h // S (5/213)	TE = 12.1; Res (5.84%)[i]; Pc (13.2%)[i] E: Res (0.77); Pc (1.73)		
hyperici grains, leaves, and flowers	33.2/323/M(15)/1.5/0.060	Q/Ru	*356*	*389*
(*Hypericum perforatum*)				
lemon balm (*Melissa officinalis* ssp.	oil: 9/323/–/–/– // S_1 (9/263), S_2 (1.5/283)		$IC_{50,LAO}$ = 6.5 μg	*217*
			$IC_{50,LAO}$= 6.8 μg	
officinalis)	30/323/–/10/–	TE = 1.9	$IC_{50,LAO,BHT}$ = 0.1 μg	
(*M. officinalis* ssp. *inodora*)	30/323/–/10/–	TE = 0.7 RA/PCAD/CA/PCA and met. esters, squalene, α-toc		
lemon balm	40/333/–/1/–	RA, CA, PCA, PCAD		*187*
(*M. officinalis*)	40/353/M +FA/1/–			
magnolia	1) 24.5/313/–/1/0.12	Mag = 1.342	*357*, *358*	*198*
(*Magnolia officinalis*)	2) 24.5/333/M (10)/1/0.12	Mag = 1.702		

Table 2 (Continued)

vegetal material (Latin name)	CO_2 SCFE conditions[b] P/T/mod/time/flow rate // S_i (P_i/T_i)	extraction yield (total extract, TE, and active compounds) (conventional solvent)[c]	antioxidant activity[d]	ref
marigold (*Calendula officinalis*)	30/323/–/ 3/0.036	TE = 5.5%; F3M (6.9)[j]	*336*, *359–361*	*168*
	50/323/–/ 3/0.036	TE = 6.0%; F3M (7.8)[j]		
	69/323/–/ 3/0.036	TE = 8.3%; F3M (8.8)[j]		
	30/323/–/ 3/35 kg/h // S_1 (6/333), S_2 (4/293)	TE = 4.7%; F3M (9.8)[j]		
	50/323/–/ 3/35 kg/h // S_1 (6/333), S_2 (4/293)	TE = 5.3%; F3M (8.0)[j]		
	80/323/–/ 3/35 kg/h // S_1 (6/333), S_2 (4/293)	TE = 5.5%; F3M (8.4)[j]		
marigold (*C. officinalis*)	30/323/E (10)/–/0.036	IRDRG (0.005)/N (0.001)/IRRG (0.002)/ FM (5.97)/FP (2.44) mg/g		*181*
	69/323/E (20)/–/0.036	IRDRG (0.017)/N (0.002)/IRRG (0.005)/ FM (6.35)/FP. (5.57) mg/g		
marigold oleoresin (*C. officinalis*)	12/313/–/3 (static)/0.066 kg/h	TE = 1.4		*127*
	15/303/–/3 (static)/0.073 kg/h	TE = 1.5		
	20/303/–/3 (static)/0.066 kg/h	TE = 2.1		
marjoram (*Origanum vulgare*)	1) 30–35/308–313/–/0.5–1/45 kg/h // S (3/278)		PV_{red} = 59%	*170*
			PV_{red} = 87%;	
	2) 50/313/–/0.5–1/45 kg/h // S (5/308)		$PV_{red,BHA:BHT}$ = 93%	
	50/368/–/0.5–1/45 kg/h // S_1 (12/348), S_2 (3.3/283)	TE = 3.2	PV_{red} = 88%;	
			$PV_{red,BHA:BHT}$ = 97%	
Hungarian marjoram (*Origanum majorana*)	45/323/–/–/– // S(4/293)	TE = 3.76%; TE_H = 5.0%; TE_E = 13.3%	PF = 1	*175*
		UA (0.10); (E: 2.1- H: 4.3)[i]; Cr (0.49);	PF_E = 1.3	
Egyptian marjoram		(E: 0.08-H:0.53)[i]	PF = 1.25	
	45/323/–/–/– // S(4/293)	TE = 5.39%; TE_H = 7.03%; TE_E = 28.9%	PF_E = 1.45	
		UA (0.19); (E:2.3- H:4.0)[i]; Cr (0.25); (E: 0.03-H:0.19)[i]		
nigella seeds (*Nigella sativa* L.)	20/313/–/2.8/0.12 // S (2.5/273)	T.O. (2.5)[i]; Tq (1.42); p-Cy (0.19)	$A_{\beta-c,LA}$ = 1.15	*220*
	30/313/–/2.8/0.12 // S (2.5/273)	T.O. (0.67)[i]; Tq (0.28); p-Cy (0.17)	$A_{\beta-c,LA}$ = 0.80	
	40/313/–/2.8/0.12 // S (2.5/273)	T.O. (0.88)[i]; Tq (0.40); p-Cy (0.15)	$A_{\beta-c,LA}$ = 0.05	
	50/313/–/2.8/0.12 // S (2.5/273)	T.O. (1.14)[i]; Tq (0.49); p-Cy (0.23)	$A_{\beta-c,LA}$ = 0.10	
			$A_{\beta-c,LA,\alpha-Toc}$ = 2.00	
osage orange tree root bark (*Maclura pomifera*)	40.5/313/M (20)/0.7/ 0.09	ECF-B (0.215); OX (0.203); ECF-C (0.241), AX (0.553); MCX (1.054); POX (0.175)	*362*, *363*	*200*
paeonia cortex (*Paeonia suffruticosa*)	24.5/313/–/0.5/0.1	Pa (1.96)	*364*, *365*	*134*
	24.5/333/–/0.5/0.13	Pa (2.35)		
passiflora leaves (*Passiflora edulis*, *P. alata*, and *P. incarnata*)	10.1/343/M (5)/0.08/–	TE (Vi/Or/Ru) = 0.630	*337*, *366*, *367*	*197*
	10.1/343/M (10)/0.08/–	TE (Vi/Or/Ru) = 0.681		
	10.1/348/M (15)/0.08/–	TE (Vi/Or/Ru) = 1.75		
	10.1/343/E (10)/0.08/–	TE (Vi/Or/Ru) = 0.559		
	10.1/343/EA (10)/0.08/–	TE (Vi/Or/Ru) = 0.220		
black pepper oleoresin (*Piper nigrum* L.)	28/318/–/–/–	RER = 5.44 (Pp: 37.6)		*390*
	28/333/–/–/–	RER = 6.47 (Pp: 39.1)	H_{red} = 65%;	
	32/318/–/–/–	RER = 5.43 (Pp: 39.4)	$TBARS_{red}$ = 52%	
		RER_{DCM} = 6.1%		
pistachio hulls (*Pistachia vera*)	35.5/328/–/0.42/–	TE = 0.11		*160*
	20.3/308/M (15)/0.42/–	TE = 0.21		
	35.5/ 308/M (5)/0.67/–	TE = 0.24		
	35.5/318/M (15)/0.25/–	TE = 0.78		
		TE_{EA} = 0.50; TE_W = 3.47		
rosemary (*Rosmarinus officinalis*)	1) 30–35/308–313/–/0.5–1/ 45 kg/h // S(3/278)		PV_{red} = 82%	*170*
			PV_{red} = 95%;	
	2) 50/313/–/0.5–1/45 kg/h // S (5/308)		$PV_{redBHA:BHT}$ = 93%	
			PV_{red} = 95%,	
	50/373 /–/ 0.5–1/45 kg/h // S_1(11.5 /358), S_2 (3.3/290)	TE = 5.2	$PV_{redBHA:BHT}$ = 97%	
			$PV_{red,beef/porksausage}$ = 96%	
rosemary (*R. officinalis*)	30/313/–/0.5/0.024–0.030	TE = 7.15	$AA_{\beta-c}$ = 5	*229*
		TE_{MW} = 6.02	$AA_{\beta-c,M-W}$ = 3	
rosemary (*R. officinalis*)	oil: 90–140/313–323/1.08	CrA; Cr	PV_{red} = 43–75%	*282*
	250–400/313–333/–/–/–		$TBARS_{red}$ = 50–68%	
rosemary (*R. officinalis*)	35.5/373/–/0.33/0.24	CrA (3.57%) (0.2–2.6)		*141*
rosemary (*R. officinalis*)	1) 25/333/0.75/0.75/0.06			*172*
	2) 25/333/M (5)/1/0.06	CrA (0.28); Cr (0.029)		
	3) 25/333/M (10)/1/0.06	A or M: CrA (0.23); Cr (0.018)		
rosemary (*R. officinalis*)	20/303/–/–/0.252 kg/h	TE = 4.1/Cm (33.9); Vbn (16.6); *t*-C (11.4)[g]	$IO_{\beta-c,LA,3h}$ = 53%	*186*
			$IO_{\beta-c,LA,3h}$ = 54%	
	20/313/–/–/0.252 kg/h	TE = 3.2/Cm (26.8); Vbn (18.1); *t*-C (8.6)[g]	$IO_{\beta-c,LA,3h}$ = 53%	
	30/303/–/–/0.252 kg/h	TE = 4.5/Cm (39.6);Vbn (20.3); *t*-C (10.3)[g]		
rosemary (*R. officinalis*)	35/333/–/–/– // S_1 (14/333), S_2 (2/293)	F_1: Rsl (3.6); Gk (11.9); Cr (5.6); CrA (66.0); MCr(1.6)[g]	$EC_{50,F1}$ = 23.6 mg/L	*247*
			$EC_{50,F2}$ = 7.5 mg/L	
		F_2: Rsl (8.0); Gk (0.13); Cr (6.4); CrA (60.7); MCr(4.6)[g]	$EC_{50,F1}$ = 33.4 mg/L	
			$EC_{50,F2}$ = 6.0 mg/L,	
	25/313/E (4)/–/– // S_1 (10/313), S_2 (2/293)	F_1: Rsl (6.0); Gk (3.14); Cr (4.1); CrA (47); MCr (1.35)[g]	$AA_{\beta-c}$ = 52.2%	
			$EC_{50,F1}$ = 6.5 mg/L,	
		F_2: Rsl (3.8); Gk (0.44); Cr (6.8); CrA (77); MCr (2.8)[g]	$AA_{\beta-c}$ = 78.6%	
			$EC_{50,F2}$ = 39.0 mg/L,	
	25/333/E (4)/– // S_1 (10/333), S_2 (2/293)	F_1: Rsl (1.8); Gk (2.26); Cr (8.7); CrA (76); MCr (2.8)[g]	$AA_{\beta-c}$ =61.1%	
			$EC_{50,F1}$ = 9.0 mg/L,	
		F_2: Rsl (51.4); Gk (0.44); Cr (10); CrA (3.9); MCr(4.0)[g]	$AA_{\beta-c}$ = 62.5%	
			$EC_{50,F2}$ = 6.9 mg/L,	

Table 2 (Continued)

vegetal material (Latin name)	CO_2 SCFE conditions[b] *P*/*T*/mod/time/flow rate // S_i (P_i/T_i)	extraction yield (total extract, TE, and active compounds) (conventional solvent)[c]	antioxidant activity[d]	ref
rosemary (*R. officinalis*)	15/333/E (7)/–/–/–//S_1 (7.5/333), S_2 (2/293)	F_1: Rsl (1.9); Gk (1.9); Cr (10.8); CrA (70.4); MCr(3.3)[g] F_2: Rsl (3.4); Gk (0.6); Cr (10.5); CrA (71.8); MCr(3.2)[g]	$AA_{\beta-c}$ = 63.7% $EC_{50,F1}$ = 12.9 mg/L $EC_{50,F2}$ = 14.2 mg/L $EC_{50,Asc.acid}$ = 2.3 mg/L	
	15/333/–/–/–// S_1 (7.5/333), S_2 (2/293)	F_1: Rsl (1.21); Gk (3.6); Cr (6.9); CrA (70.7); MCr(3.2)[g] F_2: Rsl (0.17); Gk (0.17); Cr (9.1); CrA (61.3);MCr(4.9)[g]		
rosemary (*R. officinalis* L.)	10/303/–/3/0.3 kg/h	TE = 1.6; Cm (0.025); Cn (0.001); CrA (0.236); RA (0.065)	$IO_{\beta-c,LA}$ = 88–95%	*154*
	30/303/–/3/0.3 kg/h	TE = 3.3; Cm (0.6); Cn (0.043); CrA (0.099); RA (0.187)		
	10/313/–/3/0.3 kg/h	TE = 1.0; Cm (0.26); Cn (0.012); CrA (0.136); RA (0.047)		
	30/313/–/3/0.3 kg/h	TE = 5.0; Cm (0.44); Cn (0.029); CrA (1.073); RA (0.124)		
		TE_{HD} = 1.8; Cm (1.22); Cn (0.23); CrA (0.117); RA (0.002)	$IO_{\beta-c,LA,control}$ = 42%	
		TE_E = 15.0; E: Cm (0.51); Cn (0.06); CrA (1.092); RA (0.398)		
		TE_H = 8.6; H: Cm (1.07); Cn (0.18)		
sage (*Salvia officinalis*)	1) 30–35/308–313/–/0.5–1/ 45 kg/h/S (3/278)		PV_{red} = 86%	*170*
	2) 50/313/–/0.5–1/45 kg/h/S (5/308)		PV_{red} = 94%	
	50/368/–/0.5–1/45 kg/h/ S_1 (12/353), S_2 (3.5/ 288)	TE = 5.7	PV_{red} = 95% $PV_{red,BHA:BHT}$ = 93–97%	
sage (*S. officinalis* L.)	30/313/–/0.5/0.024–0.030	TE = 5.02 TE_{MW} = 8.73	$AA_{\beta-c}$ = 4 $AA_{\beta-c,M-W}$ = 2	*229*
sage (*S. officinalis* L.)	25/373/E(1)/–/3 kg/h // S_1 (20/313), S_2 (10/313), S_3 (5/313)	TE = 21.81%; F_1 (16.01)/ F_2 (2.05)/F_3 (2.75)	PF_{F1} = 2.06; PF_{F2} = 2.03; PF_{F3} = 2.76	*194*
	35/373/–/–/3 kg/h // S_1 (25/313), S_2 (10/313), S_3 (5/313)	TE = 12.74%; F_1 (1.93)/ F_2 (5.83)/F_3 (4.98)	PF_{F1} = 2.12; PF_{F2} = 2.88; PF_{F3} = 2.78	
	35/373/E (1)/–/3 kg/h // S_1 (30/313), S_2 (10/313), S_3 (5/313)	TE = 46.26%; F_1 (024)/ F_2 (27.50)/F_3 (18.52)	PF_{F1} = 1.13; PF_{F2} = 1.59; PF_{F3} = 1.72	
St. John's wort (*H. perforatum* L.)	7/295/–/–/8 kg CO_2/kg herb	TE = 37 g/kg		*383*
	30/313/–/–/8 kg CO_2/kg herb	TE = 50 g/kg		
	30/323/–/–/8 kg CO_2/kg herb	TE = 64 g/kg		
St. John's wort (*H. perforatum* L. ssp. *angustifolium*)	8/288/–/2.5/53.5 // S (1.5/293)	TE = 1.04%; BDCA (6.71%)[g]	*368–370*	*167*
	10/313/–/2.5/53.5 // S (1.52/293)	TE = 1.40%; BDCA (13.44%)[g]		
	35/313/–/2.5/53.5 // S (1.5/293)	TE = 3.47%		
sea buckthorn (*Hippophaë rhamnoides* L.)	30/318/–/1/–	TE = 13	*314*, *371*	*191*
schisandra seeds and leaves (*Schizandra chinensis*)	40/328/–/ 1/–	seeds: lignans, 92.0–100.0; PE, 96.2–97.7 leaves: lignans, 23.8–28.8; PE, 15.1–16.8	*372*	*142*
schisandra fruits (*S. chinensis*)	24.5/313/–/0.5/0.12	DEO (0.449%)		*134*
	24.5/333/M(10)/0.5/0.12	DEO (0.483%)		
black sesame seed (*Sesamum indicum* L.)	20/328/–/3/25 // S_1 and S_2	TE = 50.41	EC_{50} = 84 μg/mmol DPPH $AR_{FTC,1g/L}$ = 67%	*161*
	30/308/–/3/15 // S_1 and S_2	TE = 51.56	EC_{50} = 66 μg/mmol DPPH $AR_{FTC,1g/L}$ = 71%	
	40/308/–/3/25 // S_1 and S_2	TE = 51.83	EC_{50} = 66 μg/mmol DPPH $AR_{FTC,1g/L}$ = 66%	
		TE_H = 33.31	$EC_{50,H}$ = 105 μg/mmol DPPH $EC_{50,BHT}$ = 5 μg/mmol DPPH $AR_{FTC,1g/LH}$ = 35% $AR_{FTC,0.1g/LBHT}$ = 80%	
black sesame seed (*S. indicum* L.)	20/308/–/3/0.15		EC_{50} = 114 μg/mL $EC_{50,Trolox}$ = 5.30 μg/mL $EC_{50,BHA}$ = 12.0 μg/mL $EC_{50,H}$ = 78.3 μg/mL $EC_{50,E}$ = 13.3 μg/mL $AR_{FTC,1g/L}$ = 67% $AR_{FTC,0.1g/LTrolox}$ = 52% $AR_{FTC,0.1g/LBHA}$ = 75% $AR_{FTC,1g/LH}$ = 24% $AR_{FTC,0.1g/LE}$ = 80%	*391*
soybean flour (*Glycine max*)	36/313/M (10)/0.5/0.03	G (14.31); Ge (0.83); Dz (13.62)[k]	*373*, *374*	*199*
	36/323/M (10)/0.5/0.03	G (53.6); Ge (1.71); Dz (30.93)[k]		
	36/333/M (10)/0.5/0.03	G (17.18); Ge (0.54); Dz (6.00)[k]		
	20/343/M (10)/0.5/0.03	G (51.94); Ge (2.46); Dz (16.63)[k]		
	30/343/M (10)/0.5/0.03	G (24.54); Ge (1.54); Dz (7.95)[k]		
		G (205.2); Ge (4.19); Dz (*3.47*)[k]		
summer savory (*Satureja hortensis* L.)	12/313/–/2.5/53.5 // S_1 (9/288); S_2 (0.2/268); S_3 (0.1/203)	S_1: Crv (32); Lnl (24); Myc (22); Myl (21)[i] S_2: Crv (44); Lnl (12); Myl (11); γ-Tpnn (20)[i] S_3: Crv (55); γ-Tpnn (38)[i]	PF_{S1} = 0.92 PF_{S2} = 1.03 PF_{S3} = 1.05 $PF_{dryplant}$ = 1.07 $PF_{solidresidue}$ = 1.34 $PF_{steamdistilllation}$ = 0.98	*213*
sweet gale fruits (*Myrica gale* L.)	13.7–30/318/–/1/–	TE = 6.1; flavonoids (3.7–13.2)[i]	*375*, *376*	*191*

Table 2 (Continued)

vegetal material (Latin name)	CO_2 SCFE conditions[b] *P*/*T*/mod/time/flow rate // S_i (P_i/T_i)	extraction yield (total extract, TE, and active compounds) (conventional solvent)[c]	antioxidant activity[d]	ref
sweet grass (*Hierochlöe odorata*)	35/313/E (20)/2/30 2 stages: 35/313/E (20)/2/30 25/313/–/1/30	TE = 6.3; DHC (7.8); hOβDGB (1.0)[i] DHC (0.49); hOβDGB (0.06)[i] TE_A = 6.0; DHC_A (0.46); $hO\beta DGB_A$ (0.08) DHC_{H-DE} (0.58); $hO\beta DGB_{H-DE}$ (0.003)	*377*, *378*	*203*
tamarind seed coat (*Tamarindus indica* L.)	30/353/–/5/0.3 10/313/E (10)/5/0.3	0.022 mg EC/100 g 13 mg EC/100 g E (150), EA (25)	PV_{red} = 28.3%, $PV_{red,\alpha-Toc}$ = 51.2% $PV_{red,E}$ = 98.1%	*180*
tamarind seed coat (*T. indica* L.)	10/313/–/3/0.3 30/313/–/3/0.3 30/353/–/1/0.3 10/313/E (10%)/2/0.3 30/313/E (10%)/5/0.3 30/353/E (10%)/1/0.3	TE = 0.05; DPA (2.4)/EC (13.2)[l] TE = 0.12; MDB (0.3)/DPA (4.4)/EC (167)[l] TE = 0.08; HDA (0.2)/MDB (3.1)/DPA (34.6)/EC (336)[l] TE = 0.22; HDA (4.1)/MDB (5.1)/DPA (50.7)/EC (21.4)[l] TE = 0.29; HDA (4.3)/MDB (6.8)/DPA (88.5)/EC (16.4)[l] TE = 0.15; HDA (6.2)/MDB (10.1)/DPA (123.9)/EC (26.1)[l] TE_{EA} = 0.74; HDA (7.1)/MDB (7.7)/DPA (69.2)/EC (116.0)[l]	$PV_{red,\alpha/toc}$ = 94%; $PV_{red,EA}$ = 95% PV_{red} = 97% PV_{red} = 97% PV_{red} = 98%	*189*
green tea (*Camelia sinensis*)	31/333/–/–/– // S_1 and S_2 (5/297) 31/333/W (8.9% w)/ –/– 31/333/E_{aq} (18)/–/– 31/333/E_{aq} (95)/–/– 31/333/E_{aq} (99.8)/–/–	EGC (93);EGCG (18)[k] EGC (122); EGCG (83); ECG (8); EC (8); GA (10)[k] EGC (96); EGCG (34); ECG (3); EC (2); GA (3)[k] EGC (290); EGCG (510); ECG (105); EC (90); GA (7)[k] EGC (290); EGCG (492); ECG (89); EC (80); GA (7)[k] W: EGC (610); EGCG (1336); ECG (202); EC (183); GA (380)[k] E: EGC (1312); EGCG (2992); ECG (459); EC (273); GA (120)[k]	*83*	*392*
T. catappa leaves seeds	21.4/313/–/0.5/–	tannin and flavonoid glycosides	IP_{DEBTA} = 43.9–67.6% IP_{DEBTA} = 35.7–69.8% IP_{DEBTA} = 30.7–63.1% $IP_{DEBTA,\alpha-Toc}$ = 96.58%	*164*
T. catappa leaves	9/313/–/2/0.06 10/313/–/2/0.06 11/313/–/2/0.06	TE = 0.112–0.999 g/kg TE = 0.399–1.024 g/kg TE = 0.117–1.517 g/kg		*90*
thyme (*T. vulgaris*)	1) 30–35/308–313/–/0.5–1/45 kg/h // S(3/278) 2) 50/313/–/0.5–1/45 kg/h // S (5/308) 50/368 /–/ 0.5–1/45 kg/h // S_1 (12/353), S_2 (3.5/288)	TE = 2.0	PV_{red} = 76% PV_{red} = 89%; $PV_{redBHA:BHT}$ = 93% PV_{red}= 94%; $PV_{redBHA:BHT}$ = 97%	*170*
thyme (*Thymus zygis* L. *sylvestris*)	18/310/–/1.67/–	TE = 6.1 MTp (4.7); TpAlc (11.2); (Thy, Crv = 12.4); STp (1.1)		*156*
thyme (*T. vulgaris*)	30/313/–/0.5/0.024–0.030	TE = 5.46 TE_{MW} = 7.39	$AA_{\beta-c}$ = 4 $AA_{\beta-c,M-W}$ = 3	*229*
thyme leaves (*T. vulgaris*)	40/333/–/–/–	TE = 4.92 TE_E = 12.3	$IT_{0.3-0.6\%}$ = 10.1–14.2 h $IT_{E(0.3-0.6\%)}$ = 12.5–14.8 h $IT_{0.01-0.1\%BHT}$ = 9.6–14.7 h $IT_{control}$ = 8.58 h	*246*
thyme (*T. vulgaris*)	8/313/–/2.5/5.7 kg/h // S (0.15/298) 10/313/–/2.5/5.7 kg/h // S (0.15/298) 15/313/–/2.5/5.7 kg/h // S (0.15/298) 20/313/–/2.5/5.7 kg/h // S (0.15/298) 40/313/–/2.5/5.7 kg/h // S (0.15/298)	TE = 0.7; Thy (0.17)[i] TE = 2.5; Thy (0.80)[i] TE = 3.2; Thy (0.83)[i] TE = 3.8; Thy (0.85)[i] TE = 3.9; Thy (0.79)[i]	$IT_{0.6\%}$ = 14.3 h $IT_{E,0.6\%}$ = 14.8 h $IT_{BHT,0.1\%}$ = 14.7 h $IT_{control}$ = 8.6 h	*135*, *136*
turmeric oil (*Curcuma longa* L.)	30/313/–/3/0.60	TE = 5.5 (STp H)	AOP_{leaves} = 78–99% AOP_{seeds} = 99% AOP_{BHT} = 82%	*393*
turmeric (*C. longa* L.)	20/303/E:iP 1:1 (6%w)/0–1.25/0.15 kg/h 30/ 303/E:iP 1:1 (7.4%w)/1.25–2.5/0.13 kg/h	ZγA (40.1); EγA (18.2); arT (15.7); Zg (3.1)[g] ZγA (39.9); EγA (18.5); arT (16.0); Zg (2.7)[g]	$IO_{\beta c-LA,3h}$ = 41% $IO_{\beta c-LA,3h}$ = 43%	*186*
vanilla beans (*Vanilla fragrans*) dry water soaked	12/306/–/–/–	pHBA (0.2); VA (0.1); pHBAl (0.6)[g]; V (21)[i] pHBA (0.1); VA (0.1); pHBAl (0.9)[g]; V (36.3)[i] EW: pHBA (1.1); VA (1.1); pHBAl (2.7)[g]; V (20)[i]	*379*, *380*	*133*

[a] Abbreviations used: IP_{DPPH}, inhibition percentage of the DPPH (1,1-diphenyl-2-picryl hydrazyl) radical; TEAC, Trolox equivalent antioxidant capacity; AP, antioxidant potency estimated as the reciprocal value of EC_{50} evaluated with the ABTS [2,2′-azobis(2-amidinopropane)] radical; OI_{FTC}, oxidation inhibition of linoleic acid measuring peroxide value with ferric thiocyanate after 12 days; $IO_{\beta-c,LA}$, inhibition of the coupled oxidation of linoleic acid and β-carotene; $AA_{\beta-c}$, antioxidant activity during bleaching of β-carotene–linoleate solution, scale (0, low; 5, high); SO_{SOD}, superoxide radical scavenger capacity of superoxide dismutase; $RAA_{\beta-c}$, relative antioxidant activity determined by β-carotene bleaching test; $T_{inh\ inc}$, increase in the inhibition time of linoleic acid oxidation induced by the free radical initiator AAPH [2,2′-azobis(2-amidinopropane hydrochloride)]; $IC_{50,LAO}$, inhibitory concentration during linoleic acid oxidation; PV_{red}, percentage of reduction in the formation of peroxides respect to control; PF, protection factor calculated as the ratio between the induction period of the sample with additive and the control sample during vegetable oil oxidation; $A_{\beta-c,LA}$, absorbance of the β-carotene–linoleic acid system; H_{red}, percentage of reduction in the formation of hexanal respect to control; $TBARS_{red}$, percentage of reduction in the

Table 2 (Continued)

formation of TBARS with respect to control; EC_{50}, extract concentration to scavenge 50% of the DPPH radical present; AR_{FTC}, absorbance reduction with the ferric thiocyanate method on oxidation of linoleic acid during 7 days; IT, induction time determined with the Rancimat method; IP_{DEBTA}, inhibition of linoleic acid peroxidation by the DEBTA (diethyl-2-thiobarbituric acid) method; and AOP, antioxidant potency with linoleic acid in an iron/ascorbate system. Simple phenolics and derivatives. HDA, 2-hydroxy-3′,4′-dihydroxyacetophenone; *c*-A, *cis*-anethole; *t*-A, *trans*-anethole; MDB, methyl-3,4-dihydroxybenzoate; BDCA, 1,2-benzenedicarboxylic acid; BDADOE, 1,2-benzenedicarboxylic acid, dioctyl ester; *p*HBA, *p*-hydroxybenzoic acid; *p*HBAl, *p*-hydroxybenzaldehyde; CA, caffeic acid; Crv, carvacrol; DHC, 5,8-dihydroxycoumarin; MG, methyl gallate; GA, gallic acid; MGG, monogalloyl glucose; GeA, gentisic acid; Ggl, gingerol; AGC, acetoguaiacone; Pa, paeonol; DPA, 3,4-dihydroxyphenyl acetate; MEP, 2-methyl-6-ethylphenol; PCAD, protocatechualdehyde; PCA, protocatechuic acid; RA, rosmarinic acid; SlA, salicylic acid; Shl, shogaol; SA, syringic acid; SnpA, sinapic acid; Thy, thymol; UA, ursolic acid; V, vanillic acid; and V, vanillin. Flavonoids: Apg, apigenin; Apg-7-g, apigenin-7-glucoside; Ba, baicalin; Bae, baicalein; B, boldine; C, catechin; EC, epicatechin; ECG, epicatechin gallate; EGCG, epigallocatechin gallate; ECF-B, euchrestaflavanone B; ECF-C, euchrestaflavanone C; Dz, daidzein; GCG, gallocatechin gallate; G, genistin; Ge, genistein; Gk, genkwanin; HP, hyperoside; L, luteolin; Mag, magnolol; *M*SPK, *Matricaria* spiroketal; N, narcissin; Nar, naringin; Or, orientin; Q, quercetin; IRDRG, isorhamnetin-3-O-(2″,6″-dirhamnosyl)glucoside; IRRG, isorhamnetin-3-O-(2″-rhamnosyl) glucoside; Ru, rutin; Vi, vitexin; V2OR, vitexin-2″-O-rhamnoside; and W, wogonin. Xanthones: AX, alvaxanthone; MCX, macluraxanthone; POX, 8-prenyltoxyloxanthone; and OX, osajaxanthone. Terpenoids: Ch, chamazulene; MTp, monoterpene; MTpH, monoterpenes hydrocarbons; MTpn, monoterpenones; OMTp, oxygenated monoterpenes; OSTp, oxygenated sesquiterpenes; STp, sesquiterpenes; STpH, sesquiterpene hydrocarbons; TpAlc, terpenil alcohols; EγA, *E*-γ-atlantone; ZγA, *Z*-γ-atlantone; ar-T, ar-Turmerone; CrA, carnosic acid; Cr, carnosol; Cv, carvone; *t*-C, *trans*-caryophylene; FP, faradiol-3-O-palmitate; F3M, faradiol-3-O-myristate; Lnl, linalool; Myc, myrcene; Myl, myrtenol; Rsl, rosmanol; MCr, methyl carnosate; Cmr, coumarin; Cm, camphor; Lm, limonene; p-Cy, *p*-cymene; γ-Tpnn, γ-terpinene; Vbn, verbenone; Zg, zingiberene; HC, hydrocarbons; Gs, ginsenosids. Other compounds: Ana, anacardic acid; hOβDGB, 5-hydroxy-8-O-β-D-glucopyranosyl-benzopyranone; α-B, α-bisabobol; Cds, cardols; Cdn, cardanols; oHC, O-hydroxycumine; pCl, *p*-cymen-7-ol; DEO, deoxyschisandrin; Pc, piceid (resveratrol glycoside); Pp, piperine; Res, resveratrol; and Tq, thymoquinone. [b] *P* (MPa)/*T* (K)/modifier (E, ethanol; FA, formic acid; M, methanol; iP, 2-propanol; and W, water) (% v/v or % w/w)/time (h)/flow rate (L/h). Separator$_i$ (P_i/T_i). [c] Extraction yield, concentration in extract, or compound yield, expressed as weight percent of the intial material. CE, crude extract; TE, total extraction yield; and RER, relative extraction rate. In bold data for conventional solvents (DCM, dichloromethane; E, ethanol; H, hexane; W, water; DE, diethyl ether; EA, ethyl acetate; PE, pethroleum ether; SDE, simultaneous distillation–extraction with dichloromethane; and HD, hydrodistillation). [d] Antioxidant activity reported in the referenced work or, if not indicated, other works referencing antioxidant activity of the plant extracts. [e] Adsorbents: AC, activated charcoal; Se, sepiolite. [f] Symbol "+", reduction of pressure to 0.1 MPa and then repressurization to extraction conditions. [g] Relative percentage of the normalized area detected by LC-MS or GC. [h] Percent of the amount extracted by Soxhlet with ethanol. [i] Relative weight content in the extract. [j] Total oil (essential oil). [k] μg/g. [l] μg/100 g.

presents the effects of the cosolvent concentration on the extraction yield of active compounds from different plants.

Water. Water is always present when processing vegetal materials, and its effects as a cosolvent are determined by the solubility in supercritical CO_2. Water has been used as a cosolvent in several industrial applications such as the extraction of nicotine, caffeine, or vanilla. The presence of water can make the extraction of certain compounds difficult, such as t-resveratrol in methanol-modified carbon dioxide (*201*) or undesirable waxy materials (*202*).

Other Compounds. Chloroform and ethyl acetate were unsuccessfully tried as cosolvents for the extraction of antioxidants from *Passiflora* leaves (*197*). Propylene glycol was not suitable for obtaining polyphenols from chamomille, due to its low miscibility with SC-CO_2 (*169*). Caprylic acid and its methyl ester were tested for the extraction of sweet grass with lower success than ethanol (*203*). The use of cosolvents can be avoided when the selectivity of the process is reduced. Some natural lipophilic compounds could act as modifiers, as reported for the extraction of essential oils (*127*). When sweet grass previously extracted with pure CO_2 was processed with CO_2-ethanol, no additional 5,8-dihydroxycoumarin and 5-hydroxy-8-O-β-D-glucopyranoyl-benzopyranone was obtained (*203*).

The use of cosolvents and their amount should be reduced when possible to reduce the volume of hazardous solvents in the process (*133*, *203*). The modifier can be added once the selected pressure is reached (*177*, *204*). The preload addition of cosolvent allowed a higher yield of ginsenosides than the sequential addition, requiring less amount of ethanol (*190*). A decision on the type of cosolvent to be used should be made on the basis of toxicity, solvent cost, and final use of the extract. Ethanol and water are acceptable for food-grade and pharmaceutical products, but ethanol is highly flammable. Water is tasteless, cheaper, and less restrictive in terms of residual solvent, as the process remains totally clean. However, the effect of its addition on the selectivity toward other nondesired compounds should be considered.

Table 2 lists representative data on the solubility and extractability of plant compounds with antioxidant activity, and a comparison with conventional solvent extraction is also presented. The effect of the presence of cosolvent on the total extraction yield and selectivity of the active compounds is shown.

5.3. Mechanical and Thermal Conditioning. The method employed in the preparation of the sample is influential on SC-CO_2 extraction. For example, the drying technique affects both the structure of the solid matrix and the possible decomposition of the active compounds, as correlated for the antioxidant activity of products from rosemary (*205*). Many of the phenolic compounds with antioxidant activity present in vegetals are stored in vacuoles or make part of the cell wall, requiring previous mechanical, thermal, or enzymatic processing to make them available to the solvent. Ground materials allow higher yields than nonground ones, because of the facilitated mass transfer. Because most data on the extraction of antioxidants from vegetal materials using SC-CO_2 were obtained with finely conminuted particles, scarce references to limitation derived from particle size are reported. The effects of reducing particle size on the extraction yield of *Thymus vulgaris* (*135*), polyphenols from ground fruits (*191*), *Hypericum perforatum* (*167*), and chamomile flavonoids (*176*) have been reported.

The granulometry of the material to be processed is limited by the performance of the fixed bed during leaching (*2*). Decreased extraction yields when using reduced particle size were reported by Rozzi et al. (*206*) due to losses by volatilization of compounds from lemon eucalyptus and lemon grass and by Kaiser et al. (*176*) due to degradation of active compounds from chamomile flowers.

5.4. Solvent Flow Rate. The solvent flow rate affects the extraction rate of the easily accessible solute. During the initial process stages, increased solvent flow rates are expected to favor the extraction. Depending on the situation, higher solvent flow rates may cause negative (*165*), negligible, or little (*135*, *207*) or weak positive effects (*206*) on the extraction process.

5.5. Extraction Time. The data reported for this variable varied within a wide range, depending on the type of solutes to be extracted and on the operational conditions. A static extraction period (1 min up to 2 h) can be maintained before

the dynamic conditions are established (15 min up to 5 h) (*134*, *169*, *177*, *179*, *209*). Alternatively, a single extraction step for 30 min to 4 h has been employed (*80*, *210*−*212*). Prolonged processing times reduced the dependency of the extraction yields on other variables (such as pressure) as observed for marigold (*168*). Zancan et al. (*143*) reported the effect of the extraction time of gingerols and shogaols (the antioxidant compounds in ginger oleoresin) for experiments lasting between 2 and 8 h.

5.6. Separator Conditions and Recovery of Extracts. The conditions in the separators govern the fractionation of the extracts. Different densities and temperatures can be kept in the separators to obtain individual fractions by reducing the extract solubility in the fluid. The separation system is formed by a restrictor, a series of vessels, and a gas collector device, either filled with a solvent to receive the solute or without solvent to allow crystallization. The fractionation of the extracts in multiple-stage separators can solve the problems associated with the unselective extraction of compounds at high pressure. Up to three separation vessels can be connected in series to fractionate the crude extract (*193*, *194*, *213*−*215*). Two separation stages have frequently been used (*171*, *217*, *218*), and sometimes, just one was employed (*219*). When using only one separator, the selection of the operational pressure is decisive to optimize the extract yield (*220*).

Catchpole et al. (*221*), dealing with the fractionation of flavonoids, reported an improved yield with respect to laboratory scale when using low pressure in the first separator, because of the reduction of losses in the nonsoluble residue. Daukšas et al. (*194*) reported on the influence of the pressure in the three separators on the yield and antioxidant activity of sage extracts: The recovery of chlorophyll was avoided in the first separator by keeping the pressure in the range of 20−25 MPa and was reached in the second one operating at 10 MPa. However, separation of chlorophyll and the compounds of interest is not always possible just by varying the extraction pressure, temperature, or time (*203*). The crude extract obtained in a single extraction step can be fractionated by releasing pressure in two or three separators. The yield can be similar to the use of a stepwise increase of the extraction pressure but with less consumption of solvent (*171*). Precipitation of waxes can be accomplished either in the first (*169*, *171*, *217*, *222*) or in the second separator (*194*). The distribution of the fractions can be altered by selecting the pressure in the first separator, and the pressure reduction in a separator results in increased yields of the precipitated extract (*194*). Depending on the configuration, extracts with antioxidant properties could be recovered in the first stage of a system made up of one extractor and two separators (*170*).

Several possibilities have been proposed to reduce the operational costs (*223*), including: (i) modifications in pressure and/or temperature in order that the fluid leaves the supercritical region, (ii) adsorption to retain the extract and regenerate the fluid simultaneously (*14*, *18*, *125*), (iii) absorption, which requires further concentration of the extract and regeneration of the fluid, or (iv) membrane technologies such as nanofiltration or reverse osmosis (*224*−*227*). The solute−solvent separation system is usually performed in vessels, vials, or cyclone separators (*159*, *165*, *169*).

To prevent losses of extract in the solvent stream, the use of adsorption columns with Celite (*228*) or Porapak Q (*126*) or traps filled with sand (*229*) has been reported. The adsorption of pre-extracted flavonoids, tocopherols, and tocotrienols can be performed on materials suitable as cigarette filters such as cellulose acetate, sepiolite, or activated charcoal (*230*); also, glass wool can be used (*231*). Silica gels were proposed to fractionate essential oils (*232*). After each extraction, CO_2 either pure or with modifier can be flushed to remove residual extract from the transfer line. For large-scale units, reutilization of CO_2 is recommended (*2*, *32*) and was also reported for pilot plant scale (*168*, *169*). Smith et al. (*173*) proposed a pressure profile extraction, by applying intermediate depressurization steps to 0.1 MPa, to improve the cashew nut shell liquid extraction and to reduce the amount of CO_2. In this case, the dissolution of CO_2 into the shell liquid phase reduced its viscosity, and the perturbations caused in the system led to an increased available surface area of the solute. The separation vessels can be filled with glass beads to prevent solvent evaporation (*231*). The extracted material can be trapped by bubbling the effluent CO_2 in ethanol of a different purity (*168*, *169*, *181*, *188*, *190*, *192*, *203*, *233*), methanol (*157*, *159*, *198*, *199*, *231*), and the trapping system can be embedded in crushed ice (*233*). To avoid the loss of volatiles, a cryogenic trap made up of a glass coil immersed in a dry ice/acetone bath was also used (*214*). A homemade device with a needle valve and a replaceable glass vial surrounded by a cooling jacket refrigerated by gas or liquid avoided losses of material, and retention of volatile constituents was proposed (*205*). Alternatively, dichloromethane (*142*) and chloroform can be used at room temperature (*210*), whereas acetone and acetonitrile have been employed at the analytical scale (*141*).

6. EQUIPMENT AND OPERATION MODE FOR SOLIDS PROCESSING

Most of the studies were performed in batch equipments with analytical purposes. Semibatch mode (batch charging of vegetable matter and continuous flow of solvent) has also been used for the extraction of solids at analytical and preparative scales. Pressure release in the extraction vessel in discontinuous operation leads to short-term stresses in the extraction vessel, which determines the choice of materials and geometry (*6*). Continuous systems with screw press developed for oil extraction from seeds (*6*) are potentially suitable for other applications, such as the extraction of antioxidants from vegetal materials.

7. SEQUENTIAL EXTRACTION AND EXTRACT PURIFICATION

The operational SCFE conditions can be optimized to extract the different components of a solid substrate selectively, using sequential extraction and/or combinations of different technologies. SC-CO_2 has been successfully applied for a variety of purposes: (i) sequential extraction of oils and antioxidants, (ii) extraction of essential oils before extracting antioxidants with conventional solvents, (iii) removal of contaminants from crude extracts, leaving the antioxidants in the residue, and (iv) purification of antioxidants from a crude extract by concentrating the antioxidants in the extract. In alternatives i and ii, the vegetal material is directly extracted, whereas in alternatives iii and iv, extraction is carried out from a crude extract either concentrated or dried in order to improve the antioxidant and/or organoleptic qualities. Alternatives i and iii operate at low severity, favoring the extraction of oil and other lipophilic compounds, whereas alternatives ii and iv require higher pressure, temperature, and modifier concentration, allowing the extraction of antioxidant compounds. In the following paragraphs, the most important features of these operational methods are revised.

(i) A sequential or fractionated extraction SCFE starts under mild conditions to recover the oil and progressively increases

in severity to extract other compounds from the residue coming from the previous stage. Both extraction pressure and modifier concentration can be increased progressively. This stepwise increase of the extraction pressure was used to yield separately the essential oil and the more hydrophilic substances from oregano (*171*), chamomile flowers (*176*), rosemary (*234*, *235*), sage (*234*), and sweet grass (*203*). Similarly, extraction of antioxidants from coriander seeds has been carried out starting with a with low-density step CO_2 treatment (10 MPa and 313 K) to separate the oil (*27*), followed by extraction at 11.6−28.0 MPa and 311−331 K (*158*). Ashraf and Taylor (*236*) proposed the extraction of grape seed oil with SC-CO_2 modified with up to 40% methanol to extract up to 80% of the monomeric polyphenols in grape seed, and the use of pure methanol to extract dimers, trimers and higher molecular weight polyphenols. Uy et al. (*170*) proposed the sequential extraction of aromatic herbs at 30−35 MPa and the residue at 50 MPa to extract potent antioxidants. Methanol-modified SC-CO_2 has been employed to extract phenolic compounds from grape seeds after the oil extraction (*237*). Increased levels of modifier allowed the extraction of high polar compounds (*238*). Sequential extraction of rosemary leaves was proposed by Ibáñez et al. (*205*) to avoid conferring flavor and odor to the extract by the essential oil. In addition to oils, other nondesirable compounds can be extracted under mild conditions: For example, the selectivity of the solvent for removing volatile compounds, waxes, and chlorophyll from lemon balm was favored by short extraction times and/or low pressures. The effect of pressure on the extraction of green pigments has been reported to be higher than the effect of temperature (*216*).

(ii) Essential oil extraction with supercritical fluids at low pressures followed by conventional solvent extraction of the solid residue has been proposed for aniseed (*239*), *Melissa officinalis* (*218*, *240*), rosemary, and sage (*241*). Under these conditions, only the more volatile compounds and waxes are extracted in the first stage. In the processing of summer savory, prolonged extraction times operating at 12 MPa and 313 K increased the antioxidant activity in the solid residue (*213*). As in alternative i, the advantage of this sequence is the improved antioxidant activity resulting from the removal of volatile compounds and waxes. Cuticular waxes located on the surface of the plant, which could interfere with the extraction of antioxidant compounds, can be separated under mild conditions, but flavonoids, triterpenoids, and organic acids remain unextracted (*240*). A hydrothermal treatment has been proposed to extract antioxidants and antimicrobials (such as quinones) from bamboo after SC-CO_2 extraction (*177*).

(iii) Because the extraction of antioxidants with SC-CO_2 requires harsh conditions (P > 300 bar) and high percentages of modifier, organic solvents (such as methanol or ethyl acetate) were preferred to supercritical ones to produce a crude extract to be further purified by SC-CO_2. Direct SC-CO_2 extraction is not recommended for byproducts obtained at a large scale with low contents of bioactive compounds. However, supercritical CO_2 can be used for purification of the primary extract to improve both purity and biological properties without causing any thermal or chemical degradation. SC-CO_2 extraction (without modifier) can be used to remove nonpolar, nonactive compounds with limited antioxidant activity from conventional extracts, leading to a solid phase with enhanced content of the antioxidant products. The use of SC-CO_2 extraction to enhance the antioxidant activity of crude rosemary extracts by extracting the nonactive compounds (essential oil and waxes) was proposed by Hadolin et al. (*235*). The use of a cosolvent may not improve the yields. Extraction with pure SC-CO_2 at 10−15 MPa and 318.2 K removed compounds with none or low antioxidant activity from the solvent crude extract, improving the antioxidant activity and organoleptic qualities (lighter color, no odor) of the product (*242*). Deodorization of rosemary 2-propanol extracts has been successfully applied without detrimental effect in antioxidant activity or color (*155*).

(iv) Extraction of crude or commercial concentrates results in lower CO_2 consumption and higher yields than direct extraction of plant material, as reported for defatted milled grape seed (*182*) and for the ethanolic extracts from *G. biloba* (*157*). The effect was more evident for high molecular weight compounds, due probably to their lower concentration and interactions with the matrix (*182*). Utilization of SC-CO_2 has been claimed for purification of tea polyphenols as a part of a complex sequence also involving ultra- and nanofiltration, vacuum concentration, spray drying, and conventional solvent extraction (*243*). The simultaneous extraction of propolis flavonoids and cinnamic acid derivatives in ethanol-modified CO_2 and the antisolvent precipitation of high molecular mass and more polar compounds was reported (*221*).

SC-CO_2 has been successfully used to recover phenolic compounds from liquid solutions (*223*, *244*). Countercurrent contact of the solvent with solutions has been employed for processing propolis (*214*), *B. kaoi* (*215*), and orange juice (*245*). SC-CO_2 extraction of liquid streams has also been used for removing undesirable compounds, for example, for removing phenolic compounds from acid wood hydrolysates to facilitate their fermentation (*231*). The most-suited extractor configuration is a countercurrent extractor allowing the regulation of the solvent-to-feed ratio at the desired extraction pressure (*193*, *223*).

8. COMPARISON OF SC-CO_2 EXTRACTS WITH PRODUCTS FROM CONVENTIONAL SOLVENT EXTRACTION

Table 2 summarizes analytical, preparative, and industrial-scale data concerning the optimal operational conditions for producing active SC-CO_2 extracts from different substrates, allowing a comparison of extraction yield, total phenolics, or main active compounds. The operational conditions are indicated to reflect the effects of the operational variables, including extraction pressure and temperature, presence and proportion of cosolvent, extraction time, solvent flow rate, and pressure in separators (when available). The volume of the solid−liquid extraction vessels ranged from 0.2 to 8 L, including home-built equipment (*197*), even though analytical and laboratory-scale equipment, including small extraction cells (5−16 mL) as well as pilot plant scale extractors (*168*, *169*, *171*, *175*, *176*, *211*, *235*, *246*), have also been used (*158*, *160*, *168*, *169*, *172*, *182*, *205*, *208*, *210*). According to Meireles (*8*), vessels of more than 50 mL could be considered process units. The solid:liquid extractor can be filled with different inert materials such as glass beads (*242*), silica gel (*157*), kieselgur (*192*, *233*), and sea sand (*204*, *247*). The material can be maintained inside one or two baskets of nylon (*126*, *154*, *248*) or directly into the extraction cell with polypropylene wool at the top and botton (*169*), with glass wool (*194*) or with glass beads (*154*), also to fill the empty space of the extractor (*248*).

Countercurrent liquid:liquid extractors, which were eventually filled with packaging materials to increase the contact between phases (*215*, *231*), have been used for fractionating crude extracts dissolved in a suitable solvent. Literature data are available for the processing of materials containing potent antioxidants, such as rosemary and grape and wine byproducts.

Table 3. Fractionation of Phenolic Compounds with Antioxidant Activity from Plant Materials by SC-CO_2[a]

material (Latin name) solvent extracts	CO_2SCFE conditions[b] *P*/*T*/mod/time/ flow rate // S (*P*/*T*/*A*)	extraction yield, concentration in extract, or compound yield (% w/w of the crude extract)[c]	antioxidant activity[d]	ref
bupleurum root (*Bupleurum kaoi*) ethanolic extracts	20/313/–/–/– // S_1 (15/313) 20/313/–/–/– // S_2 (10/313) 20/313/–/–/– // S_3 (5/313)	TP (GAE) residue: 0.83% extract: F_1, 0.47% F_2, 1.30% F_3, 1.83%[g]	I_{LPRLH} = CE (73.5); R (43.7); F_1 (40.9); F_2 (70.0); F_3 (80.8); α-Toc (103.2) IP_{DPPH} = CE (58.6); R (53.2); F_1 (64.8); F_2 (71.1); F_3 (76.3); α-Toc (79.7) IP_{SO} = CE (37.2); R (64.8); F_1 (34.4); F_2 (74.5); F_3(99.4) IP_{OH} = CE (38); R (52); F_1(25); F_2 (52); F_3 (68)	*215*
ginkgo leaves (*G. biloba*) ethanolic extract	10/323/E (1)/0.5–1/0.06 30/323/E (5)/0.5–1/0.06 10/353/E (5)/0.5–1/0.06 30/333/E (5)/0.5–1/0.06 chloroform/acetone/ adsorption	T.E. = 0.17%[h] T.E. = 0.48%[h] T.E. = 0.44%[h] T.E. = 2.10%[h]; Q (19.6); K (8.8); *i*-R (7.5); Gk (3.1); Bb (4.2) T.E. = 1.8% of CE; Q (20.6); K (6.2); i-R (5.0); Gk (1.0); Bb (1.7)	*394–396*	*157*
ginkgo leaves (*G. biloba*) methanolic extract	18/313/–/0.5/– // S (5/298/Se[a]) 23/313/–/0.5/– // S (5/298/Se[a]) 23/313/–/0.5/– // S (5/298/AC[a])	T.E. = 100% of CE T.E. = 100% of CE	IP_{DPPH} = 11.05–12.00%, $IP_{DPPH,\ EPR}$ = 7.4% IP_{DPPH} = 11.50–12.00% IP_{DPPH} = 11.05–12.00%	*230*
grape seeds (*V. vinifera*) commercial	20/313/E (2)/–/30 20/313/E (15)/–/30 20/313/M (5)/–/30 20/313/M (15)/–/30 30/313/E (2)/–/30 30/313/E (15)/–/30 30/313/M (2)/–/30 30/313/M (15)/–/30	GA (0.02); PCA (0.02); PCAD (0.11) GA (65.96); PCA (1.07); MGG (0.39); PCAD (0.47); C (9.00); SA (2.62); EC (6.10); ECG (0.71) GA (0.54); PCA (0.19); PCAD (0.13); MG (0.96) GA (30.62); PCA (1.69); MGG (0.31); PCAD (0.54); MG (9.16); C (3.24); SA (0.40); EC (1.73) GA (0.03); PCA (0.02); PCAD (0.18); SA (0.08) GA (96.70); PCA (1.50); MGG (0.77); PCAD (0.64); C (13.91); SA (8.48); EC (6.49); ECG (0.86) PCAD (0.05);MG (0.02); SA (0.03) GA (99.73); PCA (1.73); MGG (2.14); PCAD (0.70); MG (10.50); C (22.63); SA (0.17); EC (11.66); ECG (1.14)	*315*, *344–347*	*182*
sweet orange juice (*Citrus sinensis*)	16/313/–/0.33/[b]SFR = 7/0.33/2.4 S_1 (8/308); S_2 (2/298) 16/313/–/0.33/[b]SFR = 11/0.33/2.4 S_1 (8/308); S_2 (2/298)	F_1: BA(10.6); Fvn1(18.1); Fvn2(5.6); Nr(19.6); Hs(39.9); Ng(6.1) F_2: BA (63.6); Nr (6.7); Hs (9.2); Sn (6.5); Nb (11.3); HpMF (3.3) R: BA (0.7); Fvn1 (4.6); Fvn2 (3.4); Nr (15.3); Hs (67.4); Ng (8.6) F_1: BA (73.8); Hs (26.2) F_2: BA (11.5); Hs (88.5) R: BA (49.3); Nr (12.7); Hs (33.6); Ng (4.4)	*397*, *398*	*245*, *399*
propolis ethanol extract	20/333/–/–/– // S_1 (15/313) 20/333/–/–/– // S_2 (10/313) 20/333/–/–/– // S_3 (5/313)	Flv (Glg, CAPE) (QE); CE = 9.8; R (13.7) F_1 (9.0) F_2 (8.3) F_3 (7.6)	IP_{FeCl2} (%) = E (77); R (75); F_1 (50); F_2 (48); F_3 (46) $ChE_{2g/L}$ (%) = E (48); R (83); F_1 (≈40); F_2 (30); F_3 (30) $RP_{700\ nm,0.5g/L}$ = E (0.9); R (1.1); F_1 (0.9); F_2 (0.7); F_3 (0.7) $IP_{DPPH,2g/L}$ (%) = E (75); R (93); F_1 (56); F_2 (47); F_3 (27) $IP_{SO,1g/L}$ (%) = E (90); R (85); F_1 (81); F_2 (87); F_3 (73)	*214*
propolis	25–30/333/–/–/10% w propolis // S_1 (10.5–12/333) S_2 (6–6.5/313) 25–30/333/7:3 E:W/–/ 12% w propolis // S_1 (9.5–11/313–323); S_2 (6–6.5/313)	T.E. = 30% S_1: Flv (Chr/Glg/Pbk/Pbk-A/Pcb) cinnamic acids (CnA/DMACA) S_2: essential oil		*221*
rosemary leaves (*Rosmarinus officinalis*) hemicellulases/ steam distillation/ 2-propanol	10/313/–/0.5/ 0.18–0.24 20/333/Ac(10)/0.5/0.18–0.24 20/313/E:W:Ac (10:5:10)/ 0.5/0.18–0.24 35/353/E:W:Ac(10:10:10)/ 0.5/0.30–0.40	CE: α-Pn, Lm, Lnl, Cm, Brl, α-Trp, Vbn, Nl, TrpIn, p-Cyl	IP_{DPPH} = 35.61% IP_{DPPH} = 42.86% IP_{DPPH} = 43.07% IP_{DPPH} = 41.82%	*155*, *400*
rosemary (*R. officinalis*) commercial (C) traditionally dried (TD) freeze-dried (FD) oven-dried (OD) vaccuum rotary-dried (VRD)	oil.1) 10/313/–/0.5/0.18–0.24 2) 40/333/–/0.5/0.18–0.24	F_1: Cn (3.3); Cm (9.4); Brl (21.3); Vbn (15.8); BlA (2.6)[i] F_2: Cn (11.1); Cm (13.1); Brl (14.3); Vbn(11.7); BlA(1.7)[i] F_1: Cn (12.3); Cm (40.8); Brl (7.6); Vbn (9.85), BlA (2.5)[i] F_2: Cn (18.2); Cm (21.2); Brl (5.2); Vbn (7.7); BlA (1.2)[i]	$EC_{50,F1}$ = 61.9 mg/L $EC_{50,F2}$ = 28.5 mg/L $EC_{50,F1}$ = 50.7 mg/L $EC_{50,F2}$ = 33.9 mg/L $EC_{50,F1}$ = 148.0 mg/L $EC_{50,F2}$ = 43.9 mg/L $EC_{50,F1}$ = 177.7 mg/L $EC_{50,F2}$ = 153.8 mg/L	*205*

Table 3. Fractionation of Phenolic Compounds with Antioxidant Activity from Plant Materials by SC-CO_2[a]

material (Latin name) solvent extracts	CO_2SCFE conditions[b] *P*/*T*/mod/time/ flow rate // S (*P*/*T*/*A*)	extraction yield, concentration in extract, or compound yield (% w/w of the crude extract)[c]	antioxidant activity[d]	ref
		F_1: Cn (1.6); Cm (7.0); Brl (9.59); Vbn(27.24); BlA(0.79)[i] F_2: Cn (4.8); Cm (5.7); Brl (2.2); Vbn (7.5); BlA (0.2)[i] F_1: Cn (3.9); Cm(10.25); Brl(12.7); Vbn(18.85); BlA(0.5)[i] F_2: Cn (3.1); Cm (4.8); Brl (0.4); Vbn (0.2); BlA (–)[i] F_1: Cn (2.5); Cm (6.6); Brl (11.4); Vbn (13.7); BlA (0.27)[i] F_2: Cn (1.8); Cm (5.5); Brl (7.6); Vbn (12.8); BlA (–)[i]	$EC_{50,F1}$ = 5331 mg/L $EC_{50,F2}$ = 128.4 mg/L	*205*
rosemary leaves		CE: CrA (24.6); Cr (3.98)[g]	PV = 8.25 mmol/kg	*235*
(*R. officinalis*)	10/308/–/–/10 // S (0.1/298)	CrA_R (26.21); Cr_R (3.98)[g]	PV = 10.8 mmol/kg	
commercial	10/333/–/–/10	CrA_R (25.32); Cr_R (3.92)[g]	PV = 11.0 mmol/kg	
	200/308/–/–/10	CrA_R (25.90); Cr_R (3.96)[g]	PV = 10.7 mmol/kg	
	200/333/–/–/10	CrA_R (24.93); Cr_R (3.88)[g]		
spruce acid hydrolysate (*Picia abies*)	20/313/–/4.2/0.18 L sample/h 0.30 L CO_2/h	V(25)[j]; VA (13)[j]; CnfA (91)[j]; AGC(45)[j]; p-HBA(46)[j] GPl2n (2)[j]; GP2n3l (1)[j]; GP2n (2)[j]; GPn2l (20)[j]; GP12dn (87)[j]		*231*
java tea	10/313/–/0.5/– // S (5/298) AC		IP_{DPPH} = 15.32–16.00%; $IP_{DPPH,EPR}$ = 13.6%	*230*
(*Orthosiphon spicatus*)	10/313/–/0.5/– // S (5/298) Se		IP_{DPPH} = 16.67–16.87%	
methanolic extract	10/313/–/1/– // S (5/298) Se		IP_{DPPH} = 9.05–12.00%	
wine industry byproducts	25/318/–/–/1.1 kg/h	TP (GAE) = 5.0%	$EC_{50,R}$ = 1.97 g/g DPPH $EC_{50,E}$ = 20.3 g/g DPPH	*165*
(*V. vinifera*) with stems	25/318/M (5)/–/1.1 kg/h	TP (GAE) = 5.6%	$EC_{50,R}$ = 1.73 mg/mg DPPH $EC_{50,E}$ =13.4 mg/mg DPPH	
free of stems	25/318/–/–/1.1 kg/h	TP (GAE) = 4.3%	$EC_{50,R}$ = 1.85 mg/mg DPPH	
	25/318/–/–/1.1 kg/h ethyl acetate extracts	TP (GAE) = 18.0%	$EC_{50,R}$ = 0.24 mg/mg DPPH $EC_{50,EAextract}$ = 0.85 mg/mg DPPH $EC_{50,BHT}$ = 0.15 mg/mg DPPH	

[a] Abbreviations used: I_{LPRLH}, percentage inhibition of lipid peroxidation in rat liver homogenates; IP_{DPPH}, scavenging capacity against DPPH (1,1-diphenyl-2-picryl hydrazyl) radical; $IP_{DPPH,EPR}$, percentage reduction detected with EPR (electron paramagnetic resonance); IP_{SO}, scavenging capacity against superoxide radical; IP_{OH}, scavenging capacity against hydroxyl radical; IP_{FeCl2}, inhibition of lipid peroxidation induced by $FeCl_2$-ascorbate in rat liver homogenates; ChE, chelating effect on ferrous ions; RP_{700nm}, reducing power, absorbance at 700 nm; EC_{50} (mg/L), efficient concentration of antioxidant needed to reduce by 50% the initial DPPH concentration; PV, peroxide value (sunflower oil, 7 h at 371.2 K); 5,8-DHC, 5,8-dihydroxycoumarin; AGC, acetoguaiacone; BA, benzoic acid; Bb, bilobalide; BlA, bornyl acetate; Brl, borneol; C, catechin; CAPE, caffeic acid phenethyl ester; Chr, chrysin; *cis*-A, *cis*-anethole; *trans*-A, *trans*-anethole; Cm, camphor; Cn, 1,8-cineol; CnA, cinnamic acid; CnfA, coniferyl aldehyde; Cr, carnosol; CrA, carnosic acid; DMACA, 1,1-dimethylallylcaffeic acid; EC, epicatechin; ECG, epicatechin gallate; Fvn1, flavanone 1; Fvn2, flavanone 2; GA, gallic acid; Gk, ginkgolides; Glg, galangin; GP12dn, guaiacyl-propan-1,2-dione; GP2n, guaiacyl-propan-2-one; GP2n3l, guaiacyl-propan-2-one-3-ol; GPl2n, guaiacyl-propan-1-ol-2-one; GPn2l, guaiacyl-propan-1-one-2-ol; HpMF, 3,5,6,7,8,3′,4′-heptamethoxyflavone; Hs, hesperidin; *i*-R, *iso*-rhamnetin; *i*-R, *iso*-rhamnetin; K, kaempferol; Lm, limonene; Lnl, linalool; MG, methyl gallate; MGG, monogalloyl glucose; Nb, nobiletin; Ng, naringin; Nl, nerol; Nr, narirutin; Pbk, pinobanksin; Pbk-A, pinobanksin-3-acetate; PCA, protocatechuic acid; PCAD, protocatechualdehyde; Pcb, pinocembrin; p-Cyl, *p*-cymen-8-ol; p-HBA, *p*-hydroxybenzoic acid; Q, quercetin; SA, syringic acid; Sn, sinensetin; Trpln, terpinolene; V, vanillin; VA, vanillic acid; Vbn, verbenone; α-Trp, α-terpineol; and α-Pn, α-pinene. [b] *P* (MPa)/temperature (K)/modifier (Ac, acetic acid; E, ethanol; M, methanol; and W, water) (% v)/time (h)/flow rate (L/h). S_i = conditions in separators (*P*/*T*). [c] Extraction yield, concentration in extract, or compound yield. TP, total phenolics (GAE, gallic acid equivalents; QE, quercetin equivalents); TFlv, total flavonoids; CE, crude extract; E, extract; R, residual fraction, material insoluble in SC-CO_2; F_i, fractions. [d] Antioxidant activity reported in the referenced work or, if not indicated, other works referencing antioxidant activity of the plant extracts. [e] Adsorbent: AC, activated charcoal; Se, sepiolite. [f] SFR, solvent-to-feed ratio. [g] Percentage of GAE in each fraction. [h] Percentage of crude extract. [i] Normalized areas (GC/MS) of the major compounds. [j] Percentage of difference between the initial and the final concentration in the hydrolysate.

The utilization of a flow through sensor has been proposed for these latter (*249*). **Table 3** summarizes the information available on the purification and fractionation of crude extracts. In many cases, the major compounds present in the extracts have been identified, whereas some articles mention the compounds responsible for antioxidant activity. However, it must be considered that antioxidant activity of a given major compound can be modified by the presence of minor compounds. When available, data on extraction yields, composition and antioxidant activity of extracts are presented. If the antioxidant activity of the SCFE products has not been reported in the considered paper, the publications referred to conventional solvent extracts by other authors have been included. Extracts from spices and medicinal herbs are particularly interesting because the biologically active compounds are usually potent antioxidants. Data concerning oleoresins extracted at high pressures with antioxidant activity are also included, as well as information on essential oils produced under harsh conditions, which favor the extraction of other compounds with antioxidant activity (*220*).

Lower extraction time and solvent consumption with SC-CO_2 than with other solvents was reported (*190*). The extraction yield with conventional solvents (i.e., ethanol) is sometimes higher than with SC-CO_2, due mainly to the ability of ethanol for extracting a wide scope of products, including fat soluble substances, pigments, triglycerides, and free fatty acids. This fact explains that the oxidative stability of hexane extracted oil from pumpkin seed was higher than that of the SF-CO_2 extracted one at 19 MPa (*250*). In other cases, a lower yield than conventional solvents but similar oxidative protection has been reported for SCFE. The ethanol and the SC-CO_2 extracts from thyme protected sunflower oil similarly (*246*), although ethanol provided more than double the yield. The ethanolic extracts from marjoram showed a lower extraction yield but were slightly more active than SC extracts for protecting against oil oxidation (*175*).

SC-CO_2 extraction was found advantageous over conventional liquid solvent extraction (acetone, methanol, hexane, and dichloromethane) for the processing of rosemary (with or without sonication) for analytical purposes (*141*). Higher extraction yields and/or enhanced selectivity of active com-

pounds as compared to simultaneous distillation extraction, Soxhlet, or maceration were reported for black sesame (*161*), sweet gale flavonoids (*191*), and vanillin (*133*). The yield of total extractables was slightly lower in pilot scale extractions of faradiol esters from marigold (*168*) and in the extraction of flavonoids from *M. chamomilla* when no modifier was used (*169*), but in both cases, the high-performance liquid chromatography profiles were similar to those obtained by conventional extraction methods. Similar findings have been reported for the extraction of naringin from citrus peel (*188*). However, the SC-CO_2 processing of *Eucalyptus* leaves extracts showed 20% more peaks and higher antioxidant activity than extracts produced by hydrodistillation, due to the better extraction of sesquiterpenes, light and heavy oxygenated compounds (*233*). The color of the extracts produced with SC-CO_2 has been reported to be clearer than those of products obtained with conventional solvents (*137*, *154*).

8.1. Other Properties of SC Extracts and Fractions. The potential therapeutic properties of polyphenols as antiparasitic, antioxidant, antiviral, antiinflammatory, antimicrobial, and anticarcinogenic agents are well-known and justify the utilization of plant-based formulations as regulators of cell cycle gene expression, which is altered in tumor tissues (*251*). Dietary plant metabolites can regulate the expression of several proangiogenic factors, being more efficient for prevention than synthetic drugs (*252*). In addition to the antioxidant properties, the antimicrobial activity of SCFE products is the most widely reported biological property, particularly in the extracts from aromatic herbs. Extracts of marjoram were significantly more potent than ethanol extracts for inhibiting the growth of fungi and bacteria (*219*), whereas antimicrobial activity was reported for spice extracts (*186*), ginger oleoresin (*143*), and white grape seed fractions (*237*). Antimutagenic and anticancer properties have been claimed for supercritical fluid extracts of plant and spices (*11*, *186*). The ability for causing inhibition of the proliferation of breast and lung cancer cells has been reported for ginger extracts (*143*), and cocoa hull extracts provide protection from ischemic oxidative damage (*253*). SCFE products from *T. catappa* leaves caused cytotoxicity to human hepatoma cells depending on the extraction conditions (*208*).

In conclusion, in the framework derived from the progressively stricter legal restrictions in food technologies and the increasing consumers demand for "clean" additives, the use of SC-CO_2 appears as an advantageous technology. On the basis of this assumption, the production of antioxidant extracts from vegetal material is a research field of increasing importance. By selecting the operational conditions during extraction and separation, active antioxidants with other biological activities can be produced. Information on the main topics of this field is revised in this work.

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