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Evaluation of the *status quo* of polyphenols analysis: Part II—Analysis methods and food processing effects

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Abbreviations: 2LC-ECD, two-channel liquid chromatography with electrochemical detection system; 5-CQA, 5-O-caffeoylquinic acid; APCI, atmospheric pressure chemical ionization; APPI, atmospheric pressure photoionization; ASE, accelerated solvent extraction; ATPS, aqueous two-phase system; CCC, counter-current chromatography; CEC, capillary electro chromatography; CPC, centrifugal partition chromatography; DAD, diode Array Detector; DLLME, dispersive liquid-liquid microextraction; EAE, enzyme-assisted Extraction; EAPPI-MS, extractive atmospheric pressure photoionization mass spectrometry; ECD, electron capture detection; EGCG, epigallocatechin gallate; ELISA, enzyme linked immunosorbent assay; ESI, electrospray ionization; EtOAc, ethyl acetate; EtOH, ethanol; FAB, fast-atom bombardment; FID, flame ionization detector; FRET, fluorescence resonance energy transfer; GC, gas chromatography; HHP, high hydrostatic pressure; HPCD, high-pressure carbon dioxide; HPLC, high-performance liquid chromatography; HP-TLC, high-performance-TLC; HT, hydrolyzable tannins; ITMS, ion trap mobility spectrometry; LLE, liquid-liquid extraction; LSIMS, liquid secondary ion MS; MAE, microwave assisted extraction; MALDI, matrix-assisted laser desorption/ionization; MEEKC, microemulsion electrokinetic chromatography; MeOH, methanol; MEPS, microextraction by packed sorbent; MHG, microwave hydro-diffusion and gravity; MPLC, medium pressure liquid chromatography; MS/MS, tandem mass spectrometry; MSPD, matrix solid-phase dispersion; MW, microwave processing; NMR, nuclear magnetic resonance; NPCE, negative pressure cavitation extraction; ODS, octadecylsilyl; OHP, Ohmic heat processing; PDA, photo diode array; PEF, pulse electric field; PHWE, pressurized hot water extraction; PLE, pressurized liquid extraction; PME, pectin methylesterase; PPO, polyphenol oxidase; PTLC, preparative thin layer chromatography; QqQ, triple-quadrupole; QToF, quadrupole time-of-flight; RP, reverse phase; RRLC, rapid resolution liquid chromatography; SALLE, assisted liquid–liquid extraction; SBSE, stir bar sorptive extraction; SFC, supercritical fluid chromatography; SFE, supercritical fluid extraction; SPE, solid-phase extraction; SPME, solid-phase microextraction; SSE, subcritical solvent extraction; STE, smashing tissue extraction; SWE, subcritical-water extraction; TLC, thin-layer chromatography; TOFMS, time-of-flight mass spectrometry; UAE, ultrasound-assisted extraction; UEH, UAE with healing; UHPLC, ultra-high performance liquid chromatography; US, ultrasound-assisted extraction procedure; UV, ultraviolet; UV/vis, ultraviolet-visible; VBE, vacuum-powered bubble-assisted solvent extraction.

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Abstract

Nowadays due to the concern with the environmental impact of analytical techniques and in order to reduce the ecological footprint there is a tendency to use more efficient and faster procedures that use a smaller amount of organic solvents. Polyphenols have been widely studied in plant-based matrices due to their wide and potent biological properties; however there are no standardized procedures both for sample preparation and analysis of these compounds. The second of a two-part review will carry out a critical review of the extraction procedures and analytical methods applied to polyphenols and their selection criteria over a wide range of factors in relation to commerce-associated, environmental, and economic factors. It is foreseen that in the future the analysis of polyphenols in plant-based matrices includes the use of techniques that allow the simultaneous determination of different subclasses of polyphenols using fast, sophisticated, and automated techniques that allow the minimal consumption of solvents.

KEYWORDS
chromatography, extraction, flavonoid, identification, plant-based food, polyphenol, purification, quantification

1 | INTRODUCTION

Currently there is a gap regarding the concise compilation of the most relevant information on the analysis of phenolics. This paper intends to bridge this gap. Therefore, the second of a two-part review will discuss, in a concise manner, recent and updated data related to extraction procedures, analytical techniques, and instruments for qualitative and quantitative analysis of polyphenols in plant-based matrices. The topic also addresses a current question at the frontiers of research in molecular sciences, because it will sustain the explanations for analytical behavior of phenolics on their physicochemical properties and molecular interactions. Lastly the effect of food processing in the polyphenols will also be discussed.

2 | TECHNIQUES OF EXTRACTION, PURIFICATION, AND FRACTIONATION

2.1 | Flavonoids

To date, conventional and innovative extraction techniques have been reported for the study of flavonoids during the characterization of plant extracts, bioavailability tests in model systems with animals, and for the isolation of new molecules (Costa et al., 2015; Table 1).

The maceration of the sample with solvents is a very popular method, however, little by little it has been replaced by the microwave-assisted extraction or its modifications. In the application of these techniques, it is important to control the selection of the solvents, the optimization of the temperature–extraction time, and the operating conditions of the equipment. Alcohols and aqueous solutions of alkali hydroxides or NaCl have been used as solvents. Lately the use of natural deep eutectic solvents has been proposed, which are efficient, nontoxic, and environment friendly. The purification and fractionation of flavonoids is preferred in studies related to the structural characterization of new molecules. In this situation, preference is given to fractionation in columns with silica gel and extraction in the solid state, and purification by thin layer chromatography (TLC). In many of the extraction, purification, and fractionation reports, the methodologies are validated through their analytical characteristics.

2.1.1 | Isoflavonoids

The technique of extraction of isoflavonoids from plant sources is a crucial step in the development of analytical methods. Ideal techniques have to be simple, safe, cheap, robust, and suitable for industrialized scale-up. In addition, the extraction process should guarantee a highly similar composition profile in bioactive components as the original plant material without undesired loss or changes of the chemical composition. Extraction of isoflavonoids requires preliminary identification and

TABLE 1 Techniques of extraction, purification and fractionation for flavonoids

Sample	Flavonoids	Extraction	Purification/Fractionation	Reference
Haskap berries (Lonicera caerulea L.)	**Anthocyanins**: Cyanidin 3,5-diglucoside; Cyanidin 3-glucoside; Cyanidin 3-rutinoside; Pelargonidin 3-glucoside; Peonidin 3-glucoside	UAE (80% EtOH with 0.5% formic acid; 20 min at 35 °C in ultrasound bath)		Celli, Ghanem, and Brooks (2015)
Orange and purple petals (Catharanthus roseus)	**Anthocyanins**: Petunidin 3-O-(6-O-p-coumaroyl) glucose; Malvidin 3-O-(6-O-p-coumaroyl) glucose; Hirsutidin 3-O-(6-O-p-coumaroyl) glucose; 7-O-methylcyanidin 7,3′-O-dimethylcyanidin	UAE (room temperature and 30 min); UAE with healing (UEH, 40 °C for 30 min) Natural deep eutectic solvents as 1,2-propanediol–choline chloride, lactic acid–glucose, proline–malic acid, malic acid–choline chloride, glucose–choline chloride, glucose–fructose–sucrose		Dai, Rozema, Verpoorte, and Choi (2016)
Mulberry fruit (Morus nigra)	**Anthocyanins**: Cyanidin-3-*O*-glucoside; Cyanidin-3-*O*-rutinoside; Cyanidin-3-*O*-(6″-malonyl-glucoside); Cyanidin-3-*O*-(6″-dioxalyl-glucoside)	UAE (76% MeOH in water at pH 3, 48 °C extraction temperature, 70% ultrasound amplitude, 0.7 s cycle).		Espada-Bellido et al. (2017)
Green tea leaves	**Flavanols**: Epicatechins (epicatechin, epicatechin gallate, epigallocatechin gallate); Epicatechin epimers (catechin, catechin gallate, gallocatechin gallate)	SWE for epicatechins were time-dependent and the epimers were time- and temperature-dependent. Total flavonoles at 150 °C by 5 min and 10 MPa with purified water as solvent		Ko, Cheigh, and Chung (2014)
Espresso coffee (Coffea arabica)	**Isoflavones**: Genistin, daidzein, genistein, formononetin, biochanin A.	MeOH as extraction solvent	SPE Cartridge Strata C 18 (500 mg/6 mL), Strata X (200 mg/6 mLphase), DSC-18 (500 mg/6 mL)	Caprioli et al. (2016)
Soy milks	**Isoflavones**: Daidzein, genistein, glycitein, daidzin, genistin, glycitin, acetyldaidzin, acetylgenistin, acetylglycitin, malonyldaidzin, malonylgenistin,Malonylglycitin	SALLE with NaCl and CH_3CN		Park, and Jung (2017)

Continued

TABLE 1 *Continued*

Sample	Flavonoids	Extraction	Purification/Fractionation	Reference
Haematoxylum campechianum	**Chalcones**: Sappanchalcone, 3-deoxy-sappanchalcone **Homoisoflavonoids**: HematoxylolA, 4-O-methylhematoxylol, hematoxin	Successive extractions with MeOH	Silica gel (70 - 230 mesh) and gradient of dichloromethane/MeOH, collecting nine fractions	Escobar-Ramos et al. (2017)
Piper hispidum	**Chalcones**:2ť-hydroxy-4,4ť,6ť-trimethoxychalcone, 2ť-hydroxy-4,4ť,6ť-tetramethoxychalcone, 3,2ť-dihydroxy-4,4ť,6ť-trimethoxychalcone	Extraction with 90/10% EtOH/water, resultant two extracts: aqueous and hydroalcoholic		Costa, Tavares, and de Oliveira (2016)
Aerial parts (Tephrosia substriflora)	**Flavanone**Subtriflavanonol	CH_2Cl_2/CH_3OH (1:1) by percolation	Fractionation in silica gel (hexane/ EtOAc), Sephadex LH-20 (CH_2Cl_2/CH_3OH) Purification by PTLC (n-hexane/EtOAc) or (hexane/acetone).	Muiva-Mutisya et al. (2018)
Mature blackcurrant	**Flavonols**: Myricetin; quercetin; kaempferol **Anthocyanins**: Delphinidin 3-O-β-D-glucoside; delphinidin 3-O-rutinoside; cyanidin 3-O-glucoside; cyanidin 3-O-rutinoside	60% EtOH volume fraction; 3 min homogenate time; 28.3 mL/g liquid-solid ratio; 0.3% antioxidant; pH 2.5 551 microwave irradiation power; 16.4 min microwave irradiation time		Li et al. (2016)
Bark (Akschindlium godefroyanum)	**Flavanonols**: 7,3ť,5ť-trihydroxy-5-methoxyflavanonol; 7,4ť-dihydroxy-5,3ť-dimethoxyflavanonol **Flavonol**: Geraldol **Flavanonols**: (+)-taxifolin; (+)-fustin; aromadendrin 5-methyl ether	Extraction successive with hexane, EtOAc and MeOH	TLC Column chromatography: silica gel 60 (230 to 400 mesh)pre-coated silica gel 60 PF254	Chaipukdee, Kanokmedhakul, Lekphrom, and Kanokmedhakul (2014)

Abbreviations: UAE, ultrasound-assisted extraction; SWE, subcritical-water extraction; SPE, solid phase extraction; SALLE, assisted liquid -liquid extraction; TLC, thin-layer chromatography.

collection of the samples, fragmentation, and homogenization of crude extracts. Most commonly used methods for extraction of the isoflavonoids from crude samples are similar to other polyphenols and usually include a mixture of solvents (MeOH, EtOH, CH_3CN, acetone, and H_2O). MeOH/H_2O are generally used to the ratio of 80/20, v/v, and EtOH 70 to 95%. However, due to the instability of some glycosides, mild conditions are recommended avoiding high temperatures or pressure and long extraction times. Traditional methods include infusion, decoction, percolation or maceration, extraction under reflux, and Soxhlet extraction. Nowadays these methods have been surpassed by a plethora of more efficient ones. Modern techniques combine extraction and purification of isoflavonoids and include microwave-assisted (MA) extraction, UAE, negative pressure cavitation extraction (NPCE), supercritical fluid extraction (SFE), accelerated solvent extraction (ASE) and pressurized hot water extraction (PHWE), and matrix solid-phase dispersion (MSPD). This topic has been recently reviewed and a comprehensive summary of the most interesting extraction methods is reported (Blicharski, & Oniszczuk, 2017; Bustamante-Rangel, Delgado-Zamarreno, Perez-Martin, Rodriguez-Gonzalo, & Dominguez-Alvarez, 2018); therefore, a detailed analysis of the above-mentioned techniques is beyond the scope of the present review.

2.2 | Lignans and flavonolignans

The critical point for extraction of lignans is undoubtedly solvent polarity. Lignans in aglycone form can be extracted with apolar solvents such as petroleum ether, chloroform, among others. In the glycosidic form, lignans need to be hydrolyzed usually by 1 M hydrochloric acid at 100°C for 1 hr, and then extracted with a mixture of ethyl acetate/hexane (90/10, v/v) (Lehraiki et al., 2010). Generally, plant parts rich in lignans are extracted with ethanol (90–95%) and the concentrated extract is suspended in water followed by successive partition with petroleum ether, ethyl acetate, and *n*-butanol (Lei et al., 2017), which is also applicable for flavolignans. Later, the subextracts are usually applied to Sephadex LH-20 to yield lignans. As another option, Bodoira et al. (Bodoira, Velez, Andreatta, Martínez, & Maestri, 2017) reported that the highest amount of lignans from sesame seeds was obtained through extraction with 63.5% ethanol at 220 °C under 8 MPa pressure. Actually, more sophisticated extraction methods are being recently used for lignan extraction. Arruda et al. (2019) recently demonstrated an optimized extraction method for lignans from *Piper cubeba* using UAE with 84% aqueous ethanol for 38 min (extraction rate of 82% of all of the studied lignans, highlighting clusin and cubebin, which can reach 94% extraction of their total amount from the *P. cubeba* seeds) as well as aqueous two-phase system (ATPS)-coupled UAE to extract lignans from *Zanthoxylum armatum* DC., *Magnolia officinalis* Rehder et Wilson, and *Acanthopanax senticosus* (Rupr. et Maxim) Harms (Guo, Su, Huang, Wang, & Li, 2015; Yang et al., 2013), while a solid-phase extraction with methanol was also proposed as an effective method to extract lignan derivatives from *Schisandra* fruit extract (Yang, Wang, & Sheridan, 2017).

Isolation and purification of lignans can be conventionally achieved by preparative thin-layer chromatography (PTLC; e.g., silica gel thickness 1 mm type, 60F254), ion exchange chromatography (e.g., column in the acetate counter ion form, Sephadex), and HPLC with octadecylsilyl (ODS)-reverse phase column. In this line, Chen et al. (Chen, Ji, Chen, & Li, 2019) performed a separation of lignans from *S. chinensis* on a C18 column with acidified aqueous acetonitrile gradients using HPLC or UHPLC (recovery 93.49–103.52%). On the other hand, a number of hyphenated techniques are available for lignan-rich extracts. Relevantly, separation of several flavolignans (i.e., silychristins A and B, silybins A and B, isosilybins A and B, and silydianin) from *Silybum marianum* L. as well as *Schisandra* species using ultra high-performance liquid chromatography and tandem mass spectrometry (UHPLC–MS/MS) (Jeong et al., 2018). Angeloni et al. (2018) compared three extraction methods for lignans, that is, "dilute and shoot," acidic hydrolysis, and enzymatic digestion, where enzymatic hydrolysis with Clara-Diastase led to the best recovery values for lignans (secoisolariciresinol: 97%, lariciresinol: 98%, and matairesinol: 93%). In addition to these methods, supercritical-fluid extraction (Ben Rahal, Barba, Barth, & Chevalot, 2015; Patil, Bhusari, Shinde, & Wakte, 2013), magnetic solid-phase extraction based on graphene oxide (Wu et al., 2017), microwave-assisted extraction (Lu et al., 2016; Mishra, & Aeri, 2016), vacuum-powered bubble-assisted solvent extraction (VBE; Liu et al., 2015), smashing tissue extraction (STE; Cheng et al., 2016), and micelle-mediated extraction (Lee et al., 2014) are used for extraction of lignans.

2.3 | Stilbenoids

Stilbenoids are sensitive to heat, air, light, and oxidative enzymes, and *trans* to *cis* isomerization of resveratrol occurs on exposure to visible and ultraviolet light (Akinwumi, Bordun, & Anderson, 2018). Therefore, the first step in stilbenoid extraction is to ensure that samples are protected from the light during extraction if the *trans* form is desired. In a recent review article, Fabjanowicz et al. (Fabjanowicz, Płotka-Wysyłka, & Namieśnik, 2018)

summarized that the most commonly used extraction technique for stilbenoids are solid-phase extraction (SPE), solid-phase microextraction (SPME), liquid-liquid extraction (LLE), microextraction by packed sorbent (MEPS), stir bar sorptive extraction (SBSE), and dispersive liquid-liquid microextraction (DLLME). For the identification and quantification of stilbenoids in wine using GC, Vinas et al. (Vinas, Campillo, Martínez-Castillo, & Hernández-Córdoba, 2009) developed integrated SPME that allows on-fiber derivatization that accelerates the whole process of sample preparation. Centrifugal partition chromatography (CPC) has also been efficient for isolation and fractionation of stilibenoid monomers, dimers, trimers, and tetramers (Tisserant et al., 2016). In the last couple of years, a number of eco-friendly extraction methods have been optimized and validated for the rapid high yield extraction of stilbenes,such as UAE (Piñeiro, Marrufo-Curtido, Serrano, & Palma, 2017), supercritical fluid extraction (SFE), and pressurized liquid extraction (PLE) (Zachová et al., 2018). For the isolation of new stilbenoids, which depend on matrixes like other polyphenolic compounds, ethyl-acetate, ethanol, methanol, dichloromethan have been used, among others, with subsequent fractionation and purification, mostly using Sephadex LH-20 or on semi-preparative RP-HPLC (Auberon et al., 2017; Guo et al., 2018).

2.4 | Tannins (hydrolysable tannins, condensed tannins, phlorotannins, flavono-ellagitannins)

The particular physicochemical characteristics of tannins have remarkably influenced their techniques of extraction, purification, and fractionation. Tannins are constituted by polymeric phenolic compounds with a great heterogeneity in their chemical structure but joined by the presence of numerous hydroxyl groups. Tannins are commonly classified in hydrolyzable and condensed tannins. Following hydrolysis tannins yields gallic acid, ellagic acid, or other phenolic acids based on their chemical composition (Smeriglio, Barreca, Bellocco, & Trombetta, 2017). Different factors can modify the amount of tannins present in the samples and it is essential to perform careful operations of collection, drying, and storage of initial plant material to avoid unwanted loss. The sample age and stage of development influences the levels and nature of phenolics, so, it is important that the stage of maturity of all analyzed plant parts to be as similar as possible, before collecting the material for analysis. Moreover, the samples must be maintained frozen or at 4 °C to avoid secondary reactions of oxidation due to phenol oxidase, with substantial loss of the qualitative and quantitative amounts of analyzed compounds. It is also advisable to maintain the samples under dark conditions and, if liquid nitrogen is available, to freeze the collected samples and then freeze-dry them without thawing. The dried samples may be kept in desiccators under dark and cool conditions, but it is necessary to operate carefully, because the samples are hygroscopic and freeze-dry techniques induce the breakdown of cell membranes and the release in the active form of enzymes, with the possibility of drastic changes in the amount of tannins, if storage conditions are not appropriate. In place of lyophilization, the samples can be dried at about 50 to 52 °C using a forced air oven, but avoiding temperatures higher than 55 °C, because high temperature can cause inactivation of tannins or may decrease their extractability in water/organic solvents (Makkar, 2003). Extraction techniques require first the mechanical disruption of the vegetable matrix utilizing a polytron, ultra-turrax, or mortar homogenizers, with the employment of an aqueous organic solvent to favor homogenization and extraction of tannins and their diffusion from the plant material to liquid phase, under controlled temperature conditions (below 40 °C). If the analyzed samples are rich in pigments and fat and they interfere with the next determination, they can be removed from the dried material by extracting with diethyl ether containing 1% acetic acid before carrying on extraction of tannins. Aqueous methanol (50%) or acetone (70%), along with ultrasonic water bath, are two of the most common utilized solvents for extraction, as the efficacy of the solvent is linked principally to the nature of the initial material. Once the liquid phase has been removed, the extraction can be repeated until almost all the tannins have been extracted.

2.5 | Curcuminoids

The first reports on the development of techniques for the extraction and purification of curcuminoids go back the beginning of 19th century (Basnet, & Skalko-Basnet, 2011). Organic solvent extraction of dried and powdered turmeric and the following precipitation and/or crystallization techniques were employed routinely. Regarding the similarity of curcuminoids in their chemical structure (e.g., curcumin, demethoxycurcumin, and bis-demethoxycurcumin), the initial techniques employed were lack of pure curcuminoid separation, besides the presence of other chemical contaminants in varying quantities. The discovery and worldwide employment of column chromatography throughout the beginning of the 20th century have led to the development of techniques for the separation of curcuminoids both from each other and from other chemical contaminants. Although ethanol and acetone have been shown to be the most efficient solvents for extraction, alternative organic solvents have

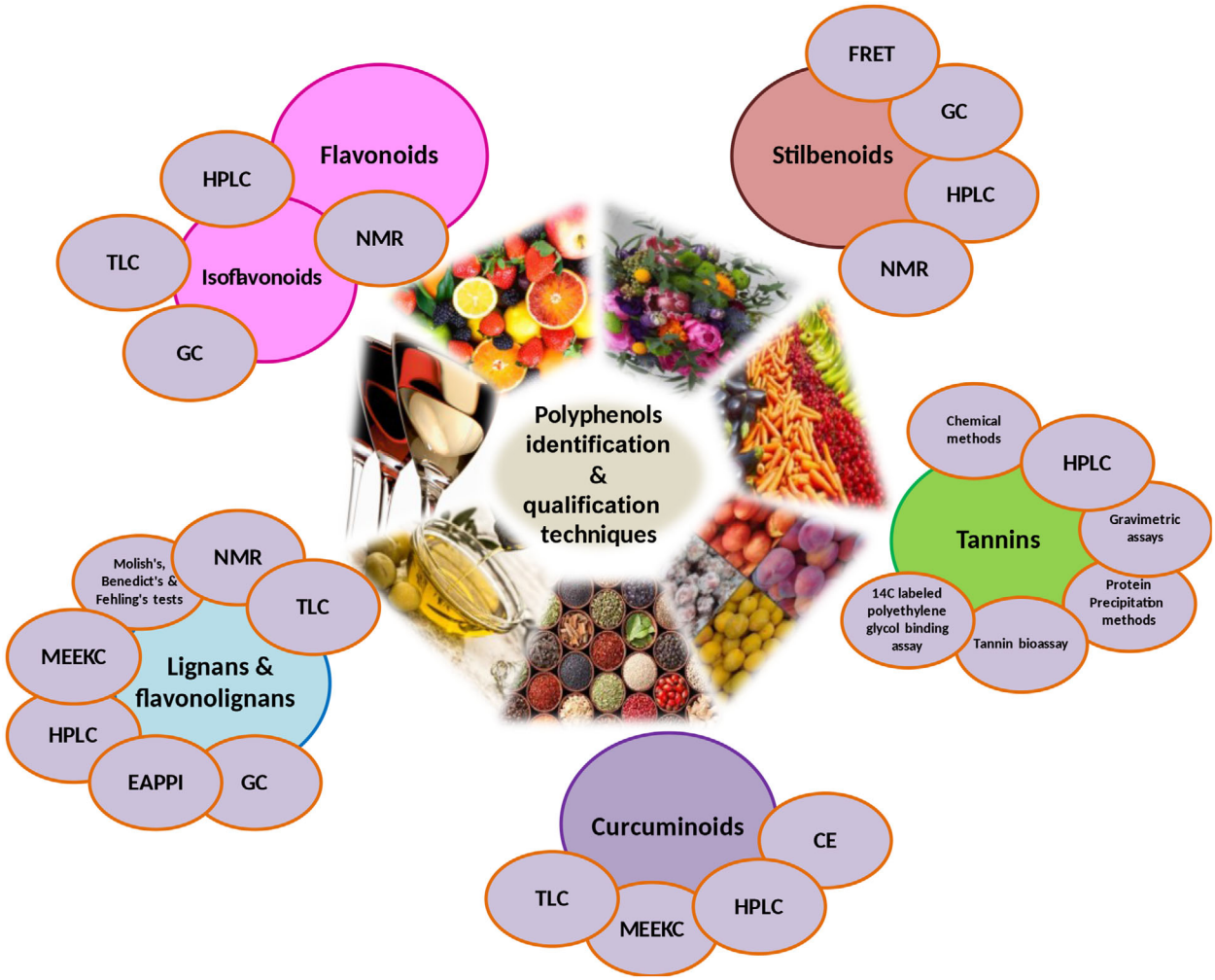


FIGURE 1 Techniques for identification and quantification of polyphenols

also been proposed (Priyadarsini, 2014). In parallel to that, various polar and nonpolar organic solvent mixtures have been suggested for the column chromatography based purification of curcuminoids (Lee, Ma, Kim, Kim, & Jin, 2012; Paulucci, Couto, Teixeira, & Freitas, 2013). It is noteworthy to state that not each extraction and purification method developed is particularly suitable for industrial purposes. This is one of the important drawbacks for food industrial applications. Indeed, successful and high-yield extraction and separation methods achieved via some chlorinated organic solvents have failed to be adapted for industrial purposes because of the limitations in residual solvent analysis and related toxicity (Kimura, Ebert, & Dodge, 1971).

It is also fundamental to evaluate small variances in extraction techniques. This involves particularly the temperature, the plant material (species), and particle size selected. Today, food industry employs the most cost-effective techniques; therefore, continuous methodologies are preferred (Priyadarsini, 2014). From this perspective, within the last two decades, Soxhlet, ultrasonic, supercritical-fluid employed, and microwave assisted extraction methodologies are the newest technologies provided, improved and worked on to effectively extract curcuminoids. Table 2 summarizes representative extraction methodologies applied to turmeric over the past 5 years.

3 | TECHNIQUES OF IDENTIFICATION AND QUANTIFICATION

The main techniques for the identification and quantification of polyphenols are summarized in Figure 1.

3.1 | Flavonoids

The qualitative and quantitative analysis of flavonoids is based on highly selective techniques such as chromatography (Table 3). The identification and quantification of

TABLE 2 Representative extraction methodologies from turmeric over the last 5 years

Method	Conditions/Yield	Reference
MAE	MeOH/water and EtOH/water (10–15 mg/g)	Bener, Özyürek, Güçlü, and Apak (2016)
UAE combined with ammonium sulfate/EtOH aqueous two-phase system (ATPS)	Ammonium sulfate/EtOH aqueous two-phase system (40–50 mg/g)	Xu et al. (2017)
Subcritical water extraction	100 °C, 30 bar and 120 min (3 mg/g material)	Perko, Ravber, Knez, and Škerget (2016)
Ultrasound assisted supercritical carbon dioxide	50 °C, 25 MPa, CO_2 flow rate of 3 mL/min with 10% cosolvent	Kimthet, Wahyudiono, Kanda, and Goto (2017)
Comparison among MAE, UAE, Soxhlet, and EAE	Higher extraction yield for Soxhlet method (6.9%) than for MAE (3.72%), UAE (3.92%), and EAE (4.1%)	Sahne, Mohammadi, Najafpour, and Moghadamnia, (2016)
ASE	ASE carried out with 20 g turmeric rhizome powder at 1,500 psi and at 50 °C, with a static time of 10 min and with three cycles. Comparision of extraction solvents: EtOH, ethyl acetate, and acetone. Highest yield using EtOH (8.4%), followed by ethyl acetate (7.4%) and acetone (6.6%). Maximum purity was recorded in acetone (46.2%), followed by EtOH (43.4%) and ethyl acetate (38.8%)	Yadav et al. (2017)
MAE	Microwave irradiation of wet turmeric damaged its plant cells wall and enhanced the yield. Curcumin extracted by MAE was related to the polarity of organic solvent.	Rezaei et al. (2016)
Pilot-scale subcritical solvent extraction	SSE optimized by varying conditions of temperature (110 to 150 °C), time (1–10 min), pressure (5-100 atm), solid-to-solvent ratio, and mixing ratio of solvent. The extraction yields of curcuminoids were: 10.49% for 50% EtOH, 13.71% for 95% EtOH and 13.96% for 100% EtOH, at the atmospheric conditions (60 °C/120 min).	Kwon and Chung (2015)
UAE versus conventional Soxhlet extraction	Extraction yield of 72% in 1 hr with the developed UAE, higher than conventional Soxhlet extraction (62% in 8 hr)	Shirsath et al. (2017)

Abbreviations: ASE, accelerated solvent extraction; EAE, enzyme-assisted extraction; MAE, microwave-assisted extraction; SSE, subcritical solvent extraction; UAE, ultrasound assisted extraction

flavonoids has been carried out by HPLC-DAD, UHPLC-UV, HPLC–MS/MS, and UHPLC-Q-TOF-MS. The detection is based on retention times, molecular masses, and MS/MS fragmentation patterns. The optimal simultaneous separation of flavonoids has been achieved by selecting the columns, operating conditions, and the detectors coupled to the equipment from liquid chromatography. Thus, resolution and exact mass measurements confirm the results and decrease the cost of the analyses. At present, it is possible to find methodologies applicable to flavonoids in general or to certain classes of flavonoids.

3.1.1 | Isoflavonoids

There are two common approaches for isoflavonoid analysis: in the native conjugated form, or in their free form following hydrolysis (acid, basic, or enzymatic). The most commonly used analytical methods for the separation of isoflavonoids are based on liquid (HPLC), thin layer (TLC), or gas (GC) chromatography, respectively.

GC is preferred for its high resolution, sensitivity, and selectivity. However, given the scarce volatility of isoflavonoids, the samples need to be previously

TABLE 3 Representative techniques of identification and quantification for flavonoids

Sample	Flavanoids	Identification	Quantification	Reference
Plasma, liver, adipose tissue, brain, amniotic fluid and placenta from rats treated with grape seed extract.	**Flavanols**: Catechin, epicatechin,and dimeric procyanidin B2	LC coupled to 6410QqQ-MS/MS In both systems the instrumental conditions were identical: Zorbax C18 (100 mm length × 2.1 mm id, 1.8 µm particle size) Elution gradient of 0.2% acetic acid and acetonitrile 350°C gas temperature, 12 L/min flow, 45 psi nebulizer gas pressure, 4,000 V capillary voltage. Operated in negative mode. TOF 135 V fragmentor and 40 to 1,200 *m/z* scan range.	Off-line µSPE-LC-TOF/MS	Arola-Arnal et al. (2013)
Haskap berries (*Lonicera caerulea* L.)	**Anthocyanins**: Cyanidin 3,5-diglucoside Cyanidin 3-glucoside Cyanidin 3-rutinoside Pelargonidin 3-glucoside Peonidin 3-glucoside	HPLC-DAD, at 520 nm, column Synergi Max-RP C12 (2501 × 4.6 mm I.d., 1.8 µm particle size) Elution gradient of 10% methanol acidified with formic acid in water and 0.1% formic acid in methanol		Celli et al. (2015)
Orange and purple petals (*Catharanthus roseus*)	**Anthocyanins**: 7-O-methylcyanidin7,3ť-O-dimethylcyanidin	UPLC -TOF-QII with an ESI interface and a diode array detector The m/z range was set to be 400 to 1,000. For ESI: 4,000 V capillary voltage, 250°C source temperature, 250°C desolvation temperature, 11.0 L/min dry gas flow, 2.0 Bar nebulizer. Kinetex C18, 100 Å to 2.10 mm column, packed with 2.6 µm particles. Elution gradient of 0.1% formic acid in water and 0.1% formic acid in methanol.		Dai et al. (2016)
Mulberry fruit (*Morus nigra*)	**Anthocyanins**: Cyanidin-3-*O*-glucoside Cyanidin-3-*O*-rutinoside Cyanidin-3-*O*-(6″-malonyl-glucoside) Cyanidin-3-*O*-(6″-dioxalyl-glucoside)	UHPLC-QToF-MS 100 to 1,200 *m/z*. For ESI in positive mode: 70 L/hr desolvation gas flow, 500 °C desolvation temperature, 10 L/hr cone gas flow, 150 °C source temperature, 700 V capillary voltage, 30 V cone voltage, 20 eV collision energy. Elution gradient of water con 2% formic acid and methanol.	UHPLC with UV-vis detector at 520 nm. Halo™ C18 LaChrom column (100 × 3 mm i.d., particle size 2.7 µm). Elution gradient of water con 5% formic acid and methanol.	Espada-Bellido et al. (2017)

(Continues)

TABLE 3 (Continued)

Sample	Flavanoids	Identification	Quantification	Reference
Isoflavone-rich supplements based on soy or redClover	**Isoflavones**:Genistein, genistin, daidzein, daidzin, glycitein, glycitin, biochanin A, formononetin, prunetin.	HPLC/MS/MS – Triple Quadrupole mass spectrometer Positive ionization, 6,000 V ion spray voltage, fragmentation by collision induced dissociation, nitrogen as collision gas Luna 3u C18 column,150 mm × 2 mm.70% methanol as HPLC eluent in isocratic mode		Andres, Hansen, Niemann, Palavinskas, and Lampen, (2015)
Espresso coffee (*Coffea arabica)*	**Isoflavones**: Genistin, daidzein, genistein, formononetin, biochanin A.	HPLC-MS/MS-Triple Quadrupole mass spectrometer 30 °C temperature column was, 350 °C temperature drying gas, 12 L/min gas flow, 60 psi nebulizer pressure, 4,000 V (negative and positive) capillary voltage Kinetex C18 column (50 × 2.10 mm i.d., 2.6 µm) Elution gradient of buffer (formic acid 0.05% - 5 mM of ammonium formate) and acetonitrile		Caprioli et al. (2016)
Soy milks	**Isoflavones**: Daidzein, genistein, glycitein, daidzin, genistin, glycitin, acetyldaidzin, acetylgenistin, acetylglycitin, malonyldaidzin, malonyl-genistin,malonylglycitin)	UHPLC-ESI-MS and UHPLC-ESI-MS/MS 15 L/min drying gas flow rate, 3 L/min nebulizer gas flow, 230 kPa CID gas pressure Kinetex C18 100 Å, 1.7 µm particle, 2.1 mm × 30 mm, Elution gradient of 0.2% formic acid in water and acetonitrile		Park and Jung (2017)
Haematoxylum campechianum	**Chalcones**: Sappanchalcone, 3-deoxy-sappanchalcone **Homoisoflavonoids**: Hematoxylol A, 4-O-methylhematoxylol, hematoxin	NMR spectra^{1}H-NMR (600 MHz), ^{13}C-NMR (150 MHz)	HPLC-DAD at 280 nm Supelcosil LC-F (25 cm x 4.6 mm, 5 µm) Elution gradient of 0.5 % TFA and water	Escobar-Ramos et al. (2017)
Plasma, urine, beer	**Prenylated chalcones**: Xanthohumol **Prenylated flavanones**: 6- prenylnaringenin 8-prenylnaringenin Isoxanthohumol	HPLC fluorescence detector and DAD Kinetex PFP column (100 A, 250 × 4.6 mm, 5 µm) Elution gradient of water with 5% formic acid and acetonitrile con 10% water/5% formic acid $\lambda_{excitation}$ 260 nm and $\lambda_{emission}$ 440 nm, PDA range 200–850 nm, 292 nm.		Sus et al. (2018)

(Continues)

TABLE 3 (Continued)

Sample	Flavanoids	Identification Quantification	Reference
Petals bicolor dahlia (*Dahlia Variabilis*)	**Chalcones**: Isoliquiritigenin, butein **Anthocyanins**: Cyanidin, pelargonidin **Flavones**:Apigenin, luteolin	HPLC at 350 nm (chalcones, flavones), 520 nm (anthocyanidins) Elution gradient of 1.5% phosphate in water and 1.5% phosphate/20% acetic acid/25% acetonitrile/water	Ohno, Hori, Hosokawa, Tatsuzawa, and Doi (2018)
Peach kernel *(Prunus persica)*	**Flavonols**: Quercetin, galangin **Phenolic acids**: protocatechuic, p-hydroxybenzoic, p-hydroxyphenylacetic, chlorogenic, p-coumaric,ferulic acids	UHPLC–LTQ OrbiTrap MS/MS 100 to 1,000 *m*/*z*. Negative ionization, 4.5 kV source voltage, −4 V capillary voltage, −59 V tube lens voltage, 275 °C capillary temperature Syncronis C18-column (100 × 2.1 mm, 1.7 μm Techniques for identification and quantification of polyphenols particle size). Elution gradient of water/0.01% acetic acid and acetonitrile	Koprivica et al. (2018)
Rice blast fungus	**Flavanones**: Sakuranetin, sternbin, naringenin	LC-MS/MS 100 to 711 m/z. 20 psi curtain gas; 450 °C temperature; 50 psi nebulizer gas 1; 50 psi GS2; 5,200 V ion spray voltage; 51.0 V declustering potential; 7.5 V entrance potential	Katsumata, Hamana, Horie, Toshima, and Hasegawa (2017)

derivatized rendering the process longer and increasing the percentage of error.

TLC and especially high-performance-TLC (HP-TLC) is an easy, flexible, and cheap separation technique for both qualitative and quantitative analysis of complex mixtures of polyphenols. The chance of various detection methods, and specific derivatization on the same plate render it an attractive method (Cimpoiu, 2006). However, HPLC using reversed phase sorbents coupled with spectrophotometric detection is one of the most commonly used techniques for separation and quantification of isoflavonoids from foods and plant sources (Raju, Kadian, Taneja, & Wahajuddin, 2015). This method permits the identification of isoflavonoids without derivatization, unlike GC, in their native form (aglycones or glycosides) and is highly efficient, sensitive, fast, and can be automated. The most popular stationary phase for isoflavonoids is C_{18} (possibly C_8 is preferred) and retention time is regulated by their hydro/lipophilic nature. The hydrophilic nature grows in the following order: free aglycones, acetyl– β–, malonyl–, and β-glucosides. Gradient flow is more suitable for complex isoflavonoid mixtures compared to the isocratic. Gradient elution commonly initiates with around 90%, v/v, of water and 10% of MeOH or CH_3CN with low percentage of weak acid (acetic, formic) that ameliorates separation and peak shape. In order to be eluted free isoflavonoids need a higher percentage of organic solvent. C_{18} stationary phase is generally used when isoflavonoids are in a mixture with other less hydrophobic phenolic substances. Other commonly used sorbents are cyanopropyl or monolithic stationary phases. Complex separation has been successfully achieved by using a double column system (2D chromatography) each column suitable for the separation of appropriate groups of similar phenols. The reduction of the particle size (<2 μm) of the sorbent along with the increase of pressure (UHPLC) improves the separation and reduces the elution time.

The most frequently used detection methods in combination with LC include UV/Vis, diode array (DAD), or mass spectrometry (MS). Detection by means of UV/Vis has been the most commonly used method over the years since all the isoflavonoids display characteristic UV spectra owing to the conjugated aromatic rings. UV/Vis spectra of the majority of isoflavonoids exhibit two main peaks, the first in the range of 240 to285 nm (Band II, associated to ring A or benzoyl moiety) and the second in the range of 300 to 400 nm (Band I, originated from ring B, or cinnamoyl moiety). Consequently, UV/Vis detection is generally performed at 254 to 260 nm, while with the use of DAD it is possible to monitor the characteristic range of Band I (Bustamante-Rangel et al., 2018). However, liquid chromatography combined with UV detection has doubtful specificity for separating and identifying isoflavonoids of highly similar structures since they frequently display quite similar UV absorption characteristics. Therefore, structural identification of the novel isoflavonoids present in plant extracts requires that the pure compounds be analyzed by NMR, mass spectrometry, and crystallography. HPLC-coupled with MS have been shown to be enormously potent tools in polyphenol analysis and identification as they enable the rapid screening of natural mixtures, using the lowest quantity of crude extracts. In addition, MS detection allows the identification and quantitation of products arising from their metabolism in biological fluids, supporting the pharmacokinetic profiling of isoflavonoids. For ionization of molecules, various methods exist including fast-atom bombardment (FAB), liquid secondary ion MS (LSIMS), electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and matrix-assisted laser desorption/ionization (MALDI). Analysis of the characteristic fragmentation pattern of isoflavonoids enables their identification. A detailed table with the different analytical methods used for the separation, detection, and identification of isoflavonoids is reported in Raju et al., 2015 (Raju et al., 2015).

Finally, immunoanalytical methods are generally applied in the clinic for the analyses of organic fluids and in routine analyses of a considerable number of samples (techniques with non-radioactive labeling, ELISA and TR-FIA).

3.2 | Lignans and flavonolignans

Lignans can be easily identified using some classic tube tests such as Molish's, Benedict's, and Fehling's tests as well as TLC, The solvent systems that can be used for TLC of lignans include ethyl acetate:methanol (1:19) or benzene:methanol (1:9) (Al-Jumaily, Al-Shimary, & Shubbr, 2012). High-performance liquid chromatography (HPLC) with octadecyl (ODS) column allows separate them. The detection is carried out with UV detector at 280 nm (Nadeem, Taj Khan, Khan, & Ajmal Shah, 2020).

For quantification of lignans, many simple (i.e., ^{13}C NMR spectroscopy; Nam, Paoli, Castola, Casanova, & Bighelli, 2011) or advanced techniques coupled with HPLC have been applied (Mudge, Paley, Schieber, & Brown, 2015; Table 4). For instance; Chen et al. (2019) developed a simple and rapid method based on matrix solid-phase dispersion (MSPD) combined with silica gel and eluted with methanol and HPLC, where HPLC-MS/MS triple quadrupole was also utilized for the quantification of lignans found in espresso coffee. More hyphenated analyses have been also employed for lignans such as a micro-matrix solid phase dispersion (MSPD) technique coupled with microemulsion electrokinetic

TABLE 4 Representative techniques of extraction, identification, purification and quantification for lignans and flavolignans

Extraction methods for lignans and flavolignans	Identification, isolation and quantification methods for lignans and flavolignans
Soxhlet extraction	^{13}C NMR spectroscopy
Ultrasound-assisted extraction (USAE)	Preparative thin layer chromatography (TLC)
Aqueous two-phase system (ATPS)-coupled USAE	HPLC-ESI-Q-TOF-MS/MS, HPLC-ESI/IT/MS
Solid-phase extraction	UPLC-MS/MS, UHPLC-Q-TOF/MS, UHPLC-PDA, UPLC-DAD-ESI-MS/MS
Supercritical-fluid extraction	HPLC-coupled with matrix solid-phase dispersion (MSPD)
Magnetic solid-phase extraction based on graphene oxide	MSPD-coupled with microemulsion electrokinetic chromatography (MEEKC)
Microwave-assisted extraction	Rapid resolution liquid chromatography (RRLC)
Vacuum-powered bubble-assisted solvent extraction (VBE)	Extractive atmospheric pressure photoionization mass spectrometry (EAPPI-MS)
Smashing tissue extraction (STE)	HPLC-electrospray ionization-mass spectrometry (HPLC-ESI-MS)
Micelle-mediated extraction	Two-channel liquid chromatography with electrochemical detection system (2LC-ECD)

chromatography (MEEKC), which was used to determine lignan derivatives in *Schisandra* fruit extract (Chu et al., 2017), rapid resolution liquid chromatography (RRLC) (Ma et al., 2011), extractive atmospheric pressure photoionization mass spectrometry (EAPPI-MS; Liu et al., 2017), HPLC–electrospray ionization–mass spectrometry (HPLC-ESI-MS) (Yi et al., 2016), two-channel LC with electrochemical detection system (2LC-ECD) (Xue, Kotani, Yang, & Hakamata, 2018) as well as even more hyphenated techniques such as HPLC–ESI–Q-TOF-MS/MS (Li et al., 2015), HPLC–ESI ion-trap tandem mass spectrometry (HPLC-ESI/IT/MS) (Taamalli et al., 2013), UHPLC-Q-TOF/MS and UHPLC-PDA (Sun et al., 2018), and UPLC–DAD–ESI–MS/MS (Bhatt, Sharma, Kumar, Sharma, & Singh, 2017).

Besides LC, some gas chromatographic techniques have been also developed to detect lignans as their trimethylsilyl ester derivatives (Willför, Smeds, & Holmbom, 2006) (Table 5). For example, lignans in wheat bran were identified and quantified by GC–ECD (Cukelj, Jakasa, Sarajlija, Novotni, & Curić, 2011), while lignan derivatives in *Cirsium vulgare* were identified by harmonized GC and LC (Boldizsár et al., 2012). The lignans in *Anthriscus sylvestris* (L.) Hoffm. were earlier also quantified by GC–MS (Koulman, Bos, Medarde, Pras, & Quax, 2001). Szokol-Borsodi, Sólyomváry, Molnár-Perl, and Boldizsár (2012) reported identification and quantification of lignans using GC–MS in the fruits of *Arctium lappa* L., *Centaurea scabiosa* L., and *Cirsium arvense* (L.) Scop.

3.3 | Stilbenoids

Stilbenoids have been identified and quantified for a decade using LC coupled with DAD (absorbance at 320 nm; González-Barrio et al., 2006) and/or MS detectors and sometimes using gas chromatography (GC) coupled with FID and MS detectors. The GC–MS is useful for the identification and quantification of already known structures present in matrices such as mixtures with another polyphenolic compounds. However, due to the long lasting and sometimes complicated derivatization process, GC-based methods are not a first choice for identification and quantification of stilbenoids. More commonly, in the present years, LC coupled with high-resolution MS detectors have been used. Although other forms of ionization are in use employing soft ionization techniques such as ESI in positive or negative mode, the best results for stilbenoids depends on the nature of the compounds (Řezanka, Kolouchová, Gharwalová, & Sigler, 2018). The use of these modern MS techniques, except for quantification and identification of known structures, helps in the discovery and structural elucidation of new stilbenes. For example, Auberon, Raminoson, Soengas, Bonté, and Lobstein (2016) isolated and identified 35 stilbenoids from *Cyrtopodium paniculatum*, using rapid RP-HPLC–DAD/UV–MS/MS-based dereplication method. From chromatographic and spectrometric data of each compound, they built a stilbenoid database called Orchidatabase that simplifies and accelerates identification. The best results for

identification can be reached by complementary use of NMR-based methods and LC–MS. Tisserant et al. detected 21 flavonoids and stilbenes in grapevine hairy root cultures, including resveratrol monomers, dimers, trimers, and a tetramer using this technique (Tisserant et al., 2016). Chromatography-based methods are predominant in stilbenoid identification and quantification; however, other methods have also been developed. Díaz and co-workers determined resveratrol by photochemically induced second-derivative fluorescence coupled with liquid–liquid extraction in wine (Díaz, Merás, & Rodríguez, 2007). They found that using this approach there is no matrix effect and recoveries around 100% were obtained at different fortification levels. Recently, in order to design a simple, effective, and rapid analytical method for resveratrol determination, Li, Tan, Ye, Cao, and Zhao (2019) developed fluorescence assay for resveratrol determination in red wine based on competitive host–guest recognition. The method depends on fluorescence resonance energy transfer (FRET), via competitive supramolecular recognition, between *p*-sulfonated calix[6]arene (CX6)-modified reduced graphene oxide (CX6@RGO) and a probe-resveratrol complex. Fora probe, rhodamine B or rhodamine 123 can be used as they have a strong fluorescence signal. During the assay, its fluorescence was quenched by CX6@RGO, based on FRET. When the target molecule was added to CX6@RGO, the probe molecule was displaced by resveratrol, and a host–guest complex, CX6@RGO-resveratrol formed, turning-on the fluorescence signal. The authors suggested that this method compared with traditional LC and GC-based methods saves time, is easy to operate, and does not require sample pretreatment, but only time will show if the method reaches a wider application.

3.4 | Tannins

The complexity of these molecules requires the employment of sophisticated and proper analytical techniques of analysis, the combining of different methodologies and, often, the derivatization of the constituents to make them detectable from an analytical point of view with the result that a remarkable number of methods have been developed for their identification and quantification (Smeriglio et al., 2017). Generally, a single method is able to measure different types of tannins, due to the reaction between tannins/phenols and the utilized reagent. The most common methods are: chemical methods (Folin-Ciocalteu, Folin-Denis or Prussian blue methods, the vanillin assay, the metal complexing assay, and the acid butanol assay with and without addition of iron), protein precipitation methods, gravimetric assays, tannin bioassay (based on the in vitro gas method and inclusion of polyethylene glycol), ^{14}C-labeled polyethylene glycol binding assay and HPLC coupled with DAD or MS detector (Makkar, 2003). Folin-Ciocalteu is one of the most common and easy chemical methods to use; it is based on the reaction of phenolic structure present in the tannins with a dye, allowing the quantification of total phenols. Starting from this analysis and after physical precipitation with polyvinyl polypyrrolidone, the specific total amount of tannins is obtained from the difference between the two measurements and expressed as tannic acid equivalents. As far as condensed tannins (proanthocyanidins) are concerned, specific detection is obtained by oxidative depolymerization of condensed tannins in butanol–HCl reagent. The reaction is due to oxidative cleavage of the interflavan bonds in the presence of mineral acids, butanol, and high temperature (about 95 °C), leading to pink-colored anthocyanidins, which can be analyzed at 550 nm. The presence of water in the samples interferes with the detection method, generating a decrease in the color development. Colored pigments could also interfere with this method and they can be removed before extraction by treating the dried samples with organic solvent (such as petroleum ether containing 1% acetic acid). Moreover, also flavan-4-ols may interfere with this method and bring about the formation of a pink color without heating, making the preparation of an appropriate blank necessary. The presence of iron in the samples shows an increase of the reproducibility and sensitivity of the method. Determination of gallotannins is based on their first hydrolysis to gallic acid under acidic conditions (mainly diluted sulphuric acid) followed by colorimetric or HPLC/UHPLC determination. The colorimetric determination is based on the utilization of rhodanine methanol solution, measuring the absorbance at 520 nm, after neutralization of the acid solution, and expressing gallotannins as gallic acid equivalents. The HPLC method is based mainly on reverse phase separation (utilizing a C18 column) and utilizing, as mobile phase, a gradient of methanol or acetonitrile in acidified water, and recording the chromatograms at 280 nm (Barreca et al., 2016). It is important, during the preparation of the samples before injection, to maintain the pH of the samples below 7.0, otherwise the components present in the samples undergo oxidation. Reversed-phase HPLC on C18 or equivalent stationary phase is one of the most utilized methods for the separation and identification of anthocyanins coupled with UV–Visible, photodiode array (DAD), fluorescence, and mass detectors. In the UV–Visible spectrum, anthocyanins show two bands of absorption with maxima at 265 to 275 nm and 465 to 560 nm regions. This latter region, between 520 nm and 546 nm, is utilized for specific analysis of anthocyanins and differentiation with flavanols, flavones, and flavonols (only bands with maxima at around 280 nm and 320 nm). Another specific detection is based

on fluorescence signals (excitation wavelength = 290 nm, emission wavelength = 320 nm). Reversed-phase LC is a useful and versatile instrument of separation, but its application is limited for the analysis of high-molecular mass compounds and, in particular high-molecular proanthocyanidins can by analyzed by normal-phase chromatography (Barreca et al., 2016; Bellocco et al., 2016a). The method uses a silica normal phase column and a gradient elution as mobile phase composed of methylene chloride, methanol, formic acid, and heptanesulfonic acid, with the following elution order: proanthocyanidins, anthocyanins, and phenolics in general. On the other hand, normal-phase chromatography is less appropriate for specific identification of favan-3-ols, because the "monomer" peak also includes many non-flavanol compounds, and anthocyanin monomers, because they are eluted together in one peak. Anthocyanins and pyranoanthocyanins can be analyzed by mixed-mode ion exchange reversed phase column constituted by a basic group with positive charge embedded in a hydrophobic chain. One of the limitations of this separation and identification technique is the long time required for the execution of the analysis (about twice the time of a reverse phase separation), but, on the other hand, it is possible to achieve a clear separation, during elution, of first the anthocyanins monoglucosides, then their acetylderivates, followed by their coumaroylderivates and finally pyranoanthocyanins and polymeric compounds. Core-shell columns (such us pentafluorophenyl), employed for both HPLC and UHPLC, have shown a remarkable increase in selectivity, resolution, and throughput in each analyzed matrix, leading to low solvent consumption, detection of low amount of compounds, and high reproducibility for anthocyanin/anthocyanidin, monomeric non-anthocyanins compounds, and condensed tannins after phloroglucinolysis (Barreca et al., 2016; Bellocco et al., 2016b). RP-HPLC—DAD–ITMS analysis has been also employed for the determination of monomeric cyanidins and procyanidins (dimers and trimers). The presence of a mass analyzer can make it possible to identify, by specific m/z ratio and fragmentation pattern, B types of procyanidin dimers (characterized by an m/z of 577 $[M - H]^-$ in negative and 579 $[M + H]^+$ in positive ionization mode) and B types of procyanidin trimers (characterized by an m/z 865 $[M - H]^-$ in negative and 867 $[M + H]^+$ in positive ionization mode; Barreca et al., 2016; De Souza, Cipriani, Iacomini, Gorin, & Sassaki, 2008). Another method of determination of tannins is based on their ability to precipitate proteins (protein precipitation assays) followed by radio labeled assay (utilizing 125I-labeled bovine serum albumin), derivatization with ninhydrin or Ponceau S, after elution on paper chromatography (Makkar, 2003). The radial diffusion assay always utilizes the protein precipitation method but shows some advantages rather over paper chromatography due to its insensitivity to the presence of acetone traces. The tannins migrate through agarose gel covered by bovine serum albumin, forming a ring after tannin-protein complex formation. The diameter of this ring is utilized to quantify the protein precipitation/binding capacity of tannins (Makkar, 2003).

3.5 | Curcuminoids

Curcuminoids are UV-active substances due to the presence of double bonds, although some atoms such as oxygen or nitrogen impart UV properties to molecules. Indeed, curcuminoids display variable λ_{max} in the 350 to 500 nm range, depending on the structural variance, and the solvent system employed. Therefore, most of the current research on identification and quantification of curcuminoids employs HPLC techniques based on a reverse phase application with C18 columns (Howells et al., 2018). Moreover, curcuminoids have been shown to possess fluorometric properties (Petrova et al., 2016). From this point of view, HPLC-diode array and fluorescence detectors are employed in HPLC studies. Besides these widely employed techniques, LC–MS/MS techniques are also developed for the identification and quantification of curcuminoids (Ma, Wang, Guo, & Tu, 2015; Purpura et al., 2018). This is particularly significant to identify the metabolites of curcuminoids in plasma and urine samples. Microemulsion electrokinetic chromatography, capillary electrophoresis, and high-performance thin-layer chromatography methodologies are other techniques utilized (Anubala, Sekar, & Nagaiah, 2016; Li et al., 2014; Taha, Krawinkel, & Morlock, 2015).

4 | EFFECT OF FOOD PROCESSING IN THE POLYPHENOLS

Food processing includes a series of operations resulting in the desired food matrix modifications, in which each operation has an impact on food constituents. Consumers are particularly interested in consuming foods rich in bioactive compounds with putative health effects. For this reason, researchers operating in food technology try to optimize processing technology to preserve compounds or increase their retaining factor. Recently, particular attention has been addressed to the impact of food processing on polyphenol content in processed food.

Anthocyanins are particularly abundant in fruits and vegetable. Wine and blueberries are among the most well-known anthocyanins rich foods. These compounds possess wide biological activities. However, they are sensible to pH variation, presence of oxygen and light, high

temperature, metal ions enzymes, and sugar (Patras, Brunton, O'Donnell, & Brijesh Kumar, 2010). During fruit juice preparation, a cleavage of sugar in position C3 has been commonly observed. The resulting chalcone breaks down to benzoic acid and 2,4,6-trihydroxyphenylacetaldehyde. To minimize pigment loss, blanching is recommended before juice extraction (Skrede, Wrolstad, & Durst, 2000). However, it is important to underline that these pigments are relatively unstable in high temperature processes as an opening of pyrylium ring and chalcone formation was observed (Patras et al., 2010). During the vinification process, anthocyanin flavanols, and proanthocyanidins can react to generate the red pigments anthocyanin-flavanol and flavanol-anthocyanin that are crucial for the organoleptic properties of red wine (Shoji, 2007). The anthocyanins petunidin, malvidin, and delphinidin are almost completely lost after any type of domestic cooking methods (Rothwell et al., 2015).

Phenolic acids are also affected by processing technology depending on the food matrix. An increase of ellagic acid was detected in fruits and juices stored in modified atmosphere at a temperature of 4 °C. The increase in ellagic acid is probably due to ellagitannin hydrolysis. However, the conversion of blueberry fruits into jam determined a reduction of 20% in ellagic acid content. A reduction of chlorogenic acid content was observed when potatoes are cooked at high temperatures. On the contrary, the use of high temperature (120 to 200 °C) during extrusion processing of barley oats, wheat, or rye determined a medium increase of 250% of ferulic, syringic, and vanillic acids (Zielinski, Kozlowska, & Lewczuk, 2001). This effect is probably due to enzyme inactivation. Frequently, caffeic acid and 5-O-caffeoylquinic acid (5-CQA) are used as markers of polyphenol sensitivity to the processing activity. It is interesting to note that losses of these compounds are independent of the applied cooking process and linked to the specific food matrix. Therefore, zucchini, broccoli, and carrots are very sensitive to 5-CQA loss. However, this was balanced by an increase in caffeic acid level probably due the hydrolysis process. Generally, high temperature processes are related to a loss of polyphenol content and it is interesting to note that in a study on the effect of domestic processing (steaming, boiling, and frying) on broccoli, quercetin, and its derivatives are retained in a significant amount when steaming process was used. The same happens irrespective of the applied technique on processed onions (Rothwell et al., 2015).

A reduction in (-)-catechin bean content associated with an increase of (-)-epicatechin was observed when epimerisation occurs, which happens when temperatures exceed 70 °C (Payne, Hurst, Miller, Rank, & Stuart, 2010). Catechin content decreases with tea fermentation where polyphenol oxidase and peroxidase are able to convert these compounds in theaflavins and thearubigins. The effect of fermentation of polyphenols is not unique. In the case of fermented soy products, the production of isoflavone aglycons by microorganisms is a positive effect since these are healthy compounds (Kano, Takayanagi, Harada, Sawada, & Ishikawa, 2006). In the past 20 years, consumers demand food products that are characterized by high nutritional quality and rich in healthy compounds in which processes are minimized. For this reason, innovative non-thermal food processing techniques to guarantee food safety and an appropriate period of shelf-life have been developed. All these techniques can be used stand alone or in combination with others. Among them, one of the most commonly used is the ultrasound assisted extraction procedure (US). US applied with a frequency of 20 kHz to 10 MHz determines an acoustic cavitation, which breaks down phenols linked to membrane proteins or polysaccharides. This process was more effective than the enzymatic one. Moreover, it increased the phenol content of food matrix by an increase of hydroxylation at aromatic ring of phenol compounds as consequence of hydroxyl radical production by US.

An increase of food phenol content was observed also by using γ-irradiation process when the irradiation dose was less than 4 kGy due to activation of the enzymes that are responsible for the synthesis of phenols (Khan et al., 2018).

High hydrostatic pressure (HHP) determines high cell permeability by disruption of salt bridges, deprotonation in charged groups, and also hydrophobic bonds. A reduction in dielectric constant of water could help to achieve higher amounts of phenols. Landl et al. compared the effect of pressure of 400 and 600 MPa on apple puree and demonstrated that in spite of the initial destructive effect of high pressure, after 21 days of storage products retain a large amount of phenolic compounds (Landl, Abadias, Sárraga, Viñas, & Picouet, 2010). The significant retention of phenols with particular reference to anthocyanins by HHP technique when compared to conventional thermal procedure was observed also with strawberry puree (Patras, Brunton, Da Pieve, & Butler, 2009). High-pressure carbon dioxide (HPCD) is a non-thermal processing technology, which uses CO_2 under pressures lower than 50 MPa and temperatures between 50 and 60 °C. A controversial effect was observed since polyphenol oxidase (PPO) and pectin methylesterase (PME) are inactivated but considering the low solubility of polyphenols in CO_2 the use of a co-solvent is recommended to extract these compounds efficiently (Khan et al., 2018). A faster PPO and lipoxygenase inactivation was observed also by using ohmic heat processing (OHP) (Khan et al., 2018). This thermal process is less aggressive than the conventional one and could be used for dehydration, evaporation, blanching, and pasteurization (Boussetta, Lanoisellé, Bedel-Cloutour, & Vorobiev, 2009).

Tomato juice treated with pulse electric field (PEF) showed a high amount of quercetin and chlorogenic acid when compared to the conventional technique (Odriozola-Serrano, Soliva-Fortuny, Hernández-Jover, & Martín-Belloso, 2009). A similar situation was observed with orange juice. PEF induces cell membrane permeabilization and induces a considerable release of healthy secondary metabolites and this effect determined a high rate of extraction (Puértolas, Luengo, Álvarez, & Raso, 2012).

Microwave processing (MW) is a process in which electro-magnetic waves in the range of 300-300,000 MHz are used. Several studies have demonstrated that application of these technologies increases the amount of phenols as consequence of a reduction in PPO activity (Khan et al., 2018). Recently, microwave technology was associated with the effect of gravity. Microwave hydro-diffusion and gravity (MHG) was applied to the extraction of onion juice to optimize time of extraction and phenolic content (Zill, Abert Vian, Maingonnat, & Chemat, 2009).

The analysis of the effect of food processing on polyphenol content of food matrix is controversial. Many data are available from studies on the effect of domestic processing whereas the impact of industrial processes is still poorly investigated. Generally, operations involving high temperatures may cause polyphenol reduction or solubilization as a consequence of cellular structure disruption whereas storage processes did not cause significant polyphenol changes when the temperature was around 4 °C. The development of food processing technologies can offer new opportunities for polyphenol retention in food matrix without affecting safety, organoleptic, or nutritional quality.

5 | CONCLUSIVE REMARKS AND FUTURE TRENDS

In order to obtain reliable analytical data from polyphenol analysis, special care is required during collection, drying, and storage of the initial plant materials to avoid unwanted loss. Concerning collection, it is important to select samples with the same age and stage of development because this greatly influences the content and nature of phenolics. Moreover, to avoid the loss of polyphenols both qualitatively and quantitatively, samples should be protected from light, kept at 4 °C, or frozen to avoid secondary reactions of oxidation due to phenol oxidase. In this line, freeze-drying is frequently recommended, and samples are typically stored freeze-dried with nitrogen and at -80 °C to minimize degradation because the removal of water can expose phenolics to oxygen.

During the extraction process it is of utmost importance to control critical parameters such as the plant material (species), particle size and temperature. Nowadays due to the concern with the environmental impact of analytical techniques and in order to reduce the ecological footprint, there is a tendency to use more efficient and faster procedures that use a smaller amount of organic solvents. Some of the newer extraction procedures applied to polyphenols include microwave-assisted extraction, ultrasound assisted extraction, negative pressure cavitation extraction, supercritical fluid extraction, matrix solid-phase dispersion, accelerated solvent extraction, micelle-mediated extraction, and pressurized hot water extraction.

For fractionation and purification of the polyphenolic extracts, several techniques besides the more common procedures (such as liquid-liquid extraction, solid phase extraction, thin layer chromatography, preparative high performance chromatography), such as medium pressure liquid chromatography (MPLC), counter-current chromatography (CCC), supercritical fluid chromatography (SFC), and capillary electrochromatography (CEC) have also been used.

Regarding the identification and quantification of polyphenolds, although HPLC or UHPLC coupled with UV or DAD detectors encompass the usual separation techniques, MS detectors have been shown to be potent tools because they enable the rapid screening of natural mixtures, using a low quantity of crude extracts and allow unequivocal identification. In addition, MS detection also allows the identification and quantitation of compounds resulting from the metabolism of polyphenols in biological fluids, supporting their pharmacokinetic profiling studies. Various methods are available for the ionization of molecules including electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), atmospheric pressure photoionization (APPI), fast-atom bombardment (FAB), liquid secondary ion MS (LSIMS), and matrix-assisted laser desorption/ionization (MALDI).

Hyphenated techniques have also been widely employed for polyphenol analysis such as MSPD–MEEKC, 2LC–ECD, HPLC–APPI–MS, UHPLC–PDA, HPLC—ESI–MS, UHPLC–Q-TOF/MS, HPLC–ESI-Q-TOF-MS/MS, and, UHPLC—DAD—ESI–MS/MS. The best results for identification can be reached by complementary use of NMR-based methods.

Although polyphenolics have been widely studied in plant-based matrices due to their wide and potent biological properties, there are no standardized procedures for sample preparation and analysis of these compounds. Future trends in the analysis of polyphenols in plant-based matrices include the development of more sophisticated and automated techniques that make it possible for this difficult task to be low-solvent and low-time consuming and simultaneously identify and quantify different subclasses of polyphenols.

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AUTHOR CONTRIBUTIONS

Conceptualization of the review was carried out by A. Sanches Silva and S. M. Nabavi; Writing of the original draft was performed by A. Sanches Silva, P. Reboredo-Rodríguez, D. Sanchez-Machado, J. López-Cervantes, D. Barreca, V. Pittala, D. Samec, I. Erdogan Orhan, H. Ozan Gulcan, and K. Pandima Devi; Revision and editing of the final version was carried out by A. Sanches Silva, P. Reboredo-Rodríguez, T. Y. Forbes-Hernandez, and M. Battino; Supervision was performed by S. F. Nabavi, S. M. Nabavi, and A. Sanches Silva. All authors have read and agreed to the published version of the manuscript.

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