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COMPREHENSIVE REVIEW

Mass spectrometry-based approaches to assess the botanical authenticity of dietary supplements

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Abstract

Dietary supplements are legally considered foods despite frequently including medicinal plants as ingredients. Currently, the consumption of herbal dietary supplements, also known as plant food supplements (PFS), is increasing worldwide and some raw botanicals, highly demanded due to their popularity, extensive use, and/or well-established pharmacological effects, have been attaining high prices in the international markets. Therefore, botanical adulteration for profit increase can occur along the whole PFS industry chain, from raw botanicals to plant extracts, until final PFS. Besides the substitution of high-value species, unintentional mislabeling can happen in morphologically similar species. Both cases represent a health risk for consumers, prompting the development of numerous works to access botanical adulterations in PFS. Among different approaches proposed for this purpose, mass spectrometry (MS)-based techniques have often been reported as the most promising, particularly when hyphenated with chromatographic techniques. Thus, this review aims at describing an overview of the developments in this field, focusing on the applications of MS-based techniques to targeted and untargeted analysis to detect botanical adulterations in plant materials, extracts, and PFS.

KEYWORDS

adulteration, botanical origin, plant food supplements, targeted MS, untargeted MS

1 | INTRODUCTION

According to the European Union and the U.S. legislation, food supplements/dietary supplements are considered concentrated sources of nutrients or other substances with a nutritional or physiological effect, being ingested orally in controlled dosages with the purpose of supplementing the regular diet (Directive, 2002/46/EC [EU, 2002]; FDA, 2019). Therefore, their formulation can include vitamins, minerals, essential fatty acids, botanical species, or extracts, among other ingredients. Over time, the consumers' awareness regarding the need for a healthy diet and lifestyle has increased and, within this trend, dietary supplements have emerged as complements to the diet, contributing to the proper organism functioning. Among them, the consumption of plant food supplements (PFS) has increased, particularly in developed countries. PFS often include medicinal plants or extracts as ingredients, which are frequently used in traditional medicine based on the ancient knowledge of their deployment to treat diseases or cure lesions. Currently, the pharmacological effects of some plants' bioactive compounds are well-known, supporting their empirical use as traditional herbal medicinal products (THMP) and ingredients in PFS. Therefore, depending on the plant species included, PFS can be used for different purposes, such as weight

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loss, improving sports performance, sexual performance, brain function, and immunity, among others, or simply for health protection and wellness (Egan et al., 2011; Garcia-Alvarez et al., 2016; Vargas-Murga et al., 2011). Moreover, in addition to globalization, which contributed to the widespread distribution of these products across continents, PFS are easily available in supermarkets, herbal shops, and e-commerce, facilitating their acquisition. The rising demand and consumption of food supplements have translated into the growth of their global market, which was estimated at USD 140.3 billion in 2020 and is expected to increase at an annual growth rate of 8.6% by 2028 (GVR, 2021a). Among several ingredients, botanicals are the second-largest share of the global market of food supplements, just after vitamins, and are estimated to witness one of the largest expansions until 2028. In particular, PFS reached sales of USD 27.47 billion in 2020 and are forecasted to have an annual growth rate of 9.1% over this projected period (GVR, 2021b). All the referred aspects make PFS potential targets for economically motivated adulterations.

1.1 | Adulteration of PFS

Despite including medicinal plants as ingredients, PFS are legally considered as foods, thus not requiring a safety assessment prior to their introduction in the market, as is mandatory for THMP under Directive 2004/24/EC (EU, 2004) amending, as regards THMP, Directive 2001/83/EC (EU, 2001). Nevertheless, PFS must comply with all the food safety issues, with the corresponding responsibility relying on food business operators (Czepielewska et al., 2018). However, besides the risks inherent to the consumption of botanicals, such as possible side effects and interaction with prescription drugs, in the last decades, different studies and reports from authorities have highlighted the existence of fraudulent practices associated with PFS production and market. Such practices, aiming at increasing profits, mainly include the illegal addition of pharmaceuticals to boost the desired effect of the product and botanical adulterations. So far, different studies and alerts from the Food and Drug Administration (FDA) and the Rapid Alert System for Food and Feed (RASFF) have shown that PFS can be doped with pharmaceutical drugs to provide quick effects and increase sales. In this respect, different review papers have been previously published and can be consulted for detailed information (Rocha et al., 2016; Tucker et al., 2018). Botanical adulteration of PFS may also affect the safety of these products and is mainly related to the intentional swap or the misidentification of plant material. Due to the growing consumption of PFS, some raw botanicals highly demanded because of their extensive use, popularity, and/or well-established pharmacological effects have been attaining high prices in the international markets. Different studies have demonstrated that these valued plant materials can be substituted with other similar and lower cost plants or even nonrelated plants that are used as fillers to increase the volume of raw materials (Grazina, Amaral, & Mafra, 2020; Newmaster et al., 2013). Moreover, trade globalization of medicinal plants native from other continents combined with the vulnerability of frequently long and complex market chains makes botanical adulterations a tangible risk for PFS. Adverse effects can arise owing to the inadvertently introduced toxic compounds from the plants used as substitutes or fillers, and to cross interactions of phytochemical compounds from the adulterant plant species (Başaran et al., 2022; Haller & Benowitz, 2000; Haller et al., 2002). In fact, different injuries and illnesses caused by the intake of PFS containing undeclared plant species have been reported, being the accidental substitution of *Stephania tetrandra* with *Aristolochia fangchi* roots, which caused several deaths and kidney transplants in 1993 in Belgium, one of the most known incidents (Ekar & Kreft, 2019; Slifman et al., 1998; Vanherweghem, 1998). Considering the health risks associated with plant substitution, as well as the consequent unfair competition among producers, it is of paramount importance to detect botanical adulterations in PFS. Therefore, in recent times, efforts have been directed to the development of reliable methods to authenticate the botanical origin of both the plants used as ingredients and the final supplements to ensure the quality of these products and protect consumers' health.

1.2 | Analytical techniques for botanical authentication of PFS

The techniques typically used for botanical authentication can vary from straightforward and low-cost morphological and microscopic identification, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC) coupled to ultraviolet (UV)–Vis or diode-array detection (DAD), to more sophisticated and accurate approaches such as genetic analyses or chemical profiling mainly relying on mass spectrometry (MS) or nuclear magnetic resonance (NMR). As happens with all methodologies, each one has its own advantages and disadvantages, being more, or less, suited to be applied at different stages of the PFS production chain, from raw botanicals to plant extracts and final commercial PFS. The simplest approaches of morphological or microscopic identification boost advantages such as reduced cost and rapidity of execution but, on the other hand, require experts in taxonomy and are not suited for powder plants, which

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are commonly used as raw materials in herbal products, neither for extracts nor for PFS. TLC, high-performance TLC, and HPLC with UV or DAD require relatively accessible instrumentation, but the obtained results may not be sufficient to address the authentication analytical requirements and challenges frequently occurring when dealing with complex plant mixtures as those present in several PFS formulations. Recently, genetic analyses have been considered the most suited for species identification in raw botanicals or their mixtures. Nonetheless, their applicability to plant extracts or final formulations might be compromised due to processing and excipients that hamper or even make unfeasible the extraction of DNA molecules (Costa et al., 2015). A review on the authentication of PFS by DNA-based methods was recently published by Grazina, Amaral, & Mafra, 2020 and can be consulted for more details on the specific subject.

Overall, chemical methods can be applied to samples ranging from raw botanicals to highly processed products such as extracts and final PFS. For authentication purposes, they include mainly spectroscopic and hyphenated chromatographic techniques. The former has the advantages of being fast, nondestructive, and cost-effective (except for the instrumentation that in some cases can be expensive), but they require the use of chemometrics and the construction of models that are only reliable when a large database of spectra is used. Moreover, most spectroscopic techniques are not able to provide critical information on the chemical structure and/or quantity of the analytes. Considering the high complexity of samples such as herbal products and PFS because of their high level of metabolites, in the last decades, hyphenated techniques have been widely exploited for botanical origin authentication as they combine the advantages of chromatographic techniques with the benefits of one or more detection methods, allowing to answer complex analytical issues (Wilson & Brinkman, 2003). Hence, separation methods, such as gas chromatography (GC), liquid chromatography (LC), or capillary electrophoresis, have been coupled to different detectors, from which MS is undoubtedly preferred, being the most applied in the authentication of natural products, including medicinal plants and PFS. HPLC is considered one of the most popular and versatile chromatographic techniques used routinely to separate components before their MS analysis (Nahar et al., 2020). More recently, ultra-performance liquid chromatography (UPLC) and ultrahigh-performance liquid chromatography (UHPLC) have been increasingly preferred over HPLC because of their fastness and higher efficiency. They rely on the use of sub-2-μm-particle columns under very high pressures, providing shorter analysis time, better separation and resolution of compounds, higher sensitivity owing to their improved signal-to-noise ratio, and reduced consumption of organic solvents due to lower flow rates (Dong & Zhang, 2014; Sarangdhar & Kachave, 2022). Currently, LC–MS is being used as an advanced analytical platform to carry out either targeted or untargeted analysis, both for authenticity assessment and/or detection of adulterations. According to Ballin and Laursen (2019), targeted analysis encompasses the detection or quantification of one or more predefined analytical targets (with the term "profiling" being used for multiple targets), while untargeted analysis aims at detecting multiple and numerous unspecified targets/compounds. For this reason, this last approach is also often designated as "fingerprinting."

When the chemical profile of botanicals is previously known and marker compound(s) unique to that species have been well established, targeted analysis by LC–MS is generally chosen as the preferred option, allowing for phytochemical authentication based on the detection/quantification of the preselected markers. However, for most botanicals, such unique marker compound(s) do not exist or are still unknown. On the other hand, targeted analysis is also frequently used by some producers to analyze the known bioactive compounds of plant material for quality control (QC) purposes. Despite this approach being very relevant to estimate the pharmacological activity, its use in detecting adulterations is somehow limited, as the bioactive compounds are most frequently present in other closely related plant species as well, which in turn can become potential adulterants. Therefore, in such cases, chemical profiling to identify and quantify several characteristic (but not unique) compounds for that species and the use of fingerprinting untargeted analyses are alternatives to be considered.

With the recent advances in instrumentation, the analysis of metabolites, commonly known as metabolomics, is emerging as a powerful technology adequate to the analysis of complex matrices, such as medicinal plants and PFS, despite the inherent challenges associated with data processing of such samples. High-resolution mass spectrometry (HRMS) has undoubtedly become a primary tool in metabolomics, although other techniques such as NMR are also valuable (Hamidi, 2021; Kellogg et al., 2019; Sullivan & Crowley, 2006). In both LC–MS profiling and LC–HRMS fingerprinting/metabolomics, the variability of plant composition with climate, soil, plant part, genetic factors, storage conditions, and so forth should be taken into consideration. Therefore, for proper development of such methodologies, a crucial point regards data acquisition from a large and representative number of authenticated voucher specimens from multiple sources to encompass the natural variability characteristic of natural products. While for medicinal plants or extracts this can be more easily accomplished, for PFS each company generally has its own

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formulations with proprietary information, which adds another level of complexity in detecting fraudulent practices in PFS.

Considering that hyphenated MS is among the most promising techniques for the botanical authentication of PFS due to its high sensitivity, accuracy, resolution, and reproducibility, this review aims at providing an overview of the reports carried out on their application using either targeted or untargeted approaches and a critical assessment on their advantages and drawbacks.

2 | MS INSTRUMENTATION

MS is a robust analytical tool that measures the individual mass-to-charge ratio (*m/z*) and relative abundance of the ionic species detected and generated after their transfer in the gas phase under the application of electric fields. The *m/z* ratio of the produced ions allows the detection and/or quantification of both known and unknown compounds present in a sample and detected in the ionized form, providing information on its chemical composition by accurate mass measurement obtained by HRMS analysis (Kaklamanos et al., 2020). In the mass spectrometer system, three main elements must be considered: the ion source, the mass analyzer, and the detector. The ion source plays a very important role in the whole system as it generates the molecular ions in the gas phase from the analyte molecules. Different methods can be applied to achieve this goal, depending mainly on the type of analyte, molecular weight, and other physical–chemical properties, but also considering the type of separation technique (GC or LC) coupled to the MS system. In addition, the desired level of ionization and/or fragmentation should also be considered. Electron ionization and chemical ionization are generally applied to produce ions from volatile to moderately volatile compounds with a relatively low molecular weight, thus being frequently coupled to gas chromatography–mass spectrometry (GC–MS) (Kaklamanos et al., 2020). In LC–MS, electrospray ionization (ESI) is the ionization mode widely applied for the analysis of polar or moderately polar compounds, while for less polar compounds atmospheric pressure chemical ionization (APCI) is typically preferred (Holčapek et al., 2012; Kaklamanos et al., 2020; Parchem et al., 2019). Other soft ionization techniques based on ion-desorption approaches are also available, such as matrix-assisted laser desorption ionization (MALDI). The most commonly used analyzer coupled to MALDI is the time-of-flight (TOF) mass spectrometer. The MALDI–TOF system allows a fast and straightforward analysis with high ion detection sensitivity and covers a larger mass range. Therefore, it has been mainly applied to analyze high-molecular-weight compounds, such as proteins, peptides, and alkaloids (Cohen & Gusev, 2002; Lu & Cai, 2013). However, MALDI–TOF is less suitable for the analysis of small-molecular-weight compounds due to the high interference of matrix ions and the lower mass ranges, which could lead to a saturation of the detector, among other drawbacks (Cohen & Gusev, 2002). Therefore, it is less applied in the authentication of medicinal plants and products thereof since plant metabolites are generally small molecules. Undoubtedly, ESI is the most applied ionization technique when botanical authentication of plant material and PFS is considered. The characteristics of the most frequently used ion sources are summarized in Table 1.

The ionic species generated in the ionization source are attracted by duly optimized electric fields in the mass analyzer and separated according to their characteristics and *m/z* ratio. As for the tuning of ionization source and mass analyzer settings, it should be carefully accomplished to maximize the ion signal based on the physicochemical properties of the analytes of interest. In the case of complex mixtures, optimization of the setting should take into account the diverse properties displayed by different categories of compounds seeking the best compromise for their detection.

Among the different mass analyzers available on the market, the most used are the triple quadrupole (QQQ), the ion trap, the TOF, and the orbital ion trap (Orbitrap). They differ in the range of the *m/z* ratio covered, resolution, accuracy, and scanning rates, among other features, as shown in Table 2 (Holčapek et al., 2012; Kaklamanos et al., 2020; Zhong et al., 2022). For targeted analysis, the low-resolution platforms typically based on quadrupole and ion trap are the most commonly used mass analyzers thanks to (i) the so-called multiple reaction monitoring (MRM) acquisition mode adopted for monitoring known transitions (precursor/fragments) for each target analyte along the whole run and (ii) the lower costs required for such instrumentation. On the other hand, when untargeted analysis is needed, the preferred approach is based on HRMS that delivers accurate mass measures of the unknown compounds; this can lead to the identification and structural elucidation of the unknown molecules. This latter is being widely used for untargeted analysis in different fields and aims at metabolite profiling and chemical identification of the analytes of interest by exploiting two types of mass analyzers: TOF and the Orbitrap systems (Tables 3 and 4). The latter can switch polarity more rapidly and surpass TOF-MS in resolution power, mass accuracy, and dynamic range (Zhong et al., 2022). To accrue the full potential of the entire platform, both analyzers can be combined with a quadrupole put in the front and originating a “hybrid system” such as the Q-Orbitrap or Q-TOF solutions. This will enable the filtering of the precursor ion pass

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band, reducing other ions entering the mass analyzer and, as a result, decreasing the noise of interfering compounds and making the analysis more accurate.

Finally, the detector system has the purpose of converting the detected ions produced into electrical signals, measuring and recording the relative abundance of ionic species (Kaklamanos et al., 2020). More details on MS systems, including MS acquisition types and data preprocessing, can be consulted elsewhere (Pérez-Cova et al., 2021; Theodoridis et al., 2011, 2012; Tsai et al., 2016; Zhong et al., 2022).

3 | MS AS A TOOL FOR THE AUTHENTICATION OF PFS

3.1 | Extraction methods and sample preparation

The application of MS technology has emerged to solve several issues in the analysis of complex samples in various fields, including food analysis and natural products owing to its high-resolution power, specificity, and sensitivity (Kaklamanos et al., 2020; Wolfender et al., 2015). Nevertheless, despite the mass selectivity of the MS detector, in such samples, the separation of the analytes is always preferred to minimize possible matrix effects that can interfere with or suppress the signals of the analytes (Vaclavik et al., 2014). In the particular case of PFS, besides including one or several powdered plants and/or plant extracts, their complexity is even increased by the inclusion of several excipients, such as technological agents to act as acidifiers, stabilizers, emulsifiers, binders, sweeteners, diluents, surfactants, and preservatives, among others (Rowe et al., 2009). Therefore, the hyphenation with a preceding chromatographic step is the general approach for most available MS-based methodologies applied to the botanical authentication of medicinal plants, extracts, or PFS (Tables 3 and 4). Moreover, it is also relevant to consider the use of an accurate method design following a workflow plan that reflects the purpose of the analysis, the physicochemical properties of the analyte(s), the sample preparation and/or extraction, and the analytical method to be applied. Therefore, for botanical authentication or adulterant detection in the PFS supply chain, the first step is to define whether the study involves the determination of specific known metabolites, corresponding to a targeted analysis, or whether the analyses are intended to obtain fingerprints and/or detect unknown compounds in a nontargeted approach since this immediately impacts sample preparation and extraction. Ideally, in either case, the sample preparation and extraction procedures should involve a minimum sample handling, being as simple as

TABLE 1 Characteristics of the most frequently used ion sources in MS platforms.

Characteristics	Electron ionization (EI)	Chemical ionization (CI)	Atmospheric-pressure chemical ionization (APCI)	Electrospray ionization (ESI)	Matrix-assisted laser desorption ionization (MALDI)
Analyte phase	Gas	Gas	Liquid	Liquid	Solid
Ionization	Electron stream	Reagent gaseous ions	Soft ionization	High-electric field	Laser beam
Energy	Hard ionization	Soft ionization	Soft ionization	Soft ionization	Soft ionization
Spectra	Extensive fragments	Few fragments	Rare fragmentation	Charged ions	Charged molecular ions and charged ions
Separation	GC	GC	LC	LC and CE	LC

Abbreviations: CE, capillary electrophoresis; GC, gas chromatography; LC, liquid chromatography; MS, mass spectrometry.

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TABLE 2 Characteristics of the most frequently used mass analyzers (adapted from Holčapek et al., 2012; Kaklamanos et al., 2020; Zhong et al., 2022).

Characteristics	Quadrupole (Q)	Ion trap (IT)	Time of flight (TOF)	Orbitrap
Separation principle	Trajectory stability	Frequency	Flight time	Frequency
Ion beam	Continuous	Continuous	Pulsed	Pulsed
Mass range of m/z (u)	3000	6000	Theoretically unlimited	100,000
Resolution (FWHM)	2000	4000	5000–40,000	100,000-140,000
Scan speed	High	High	Very high	High
Accuracy	100 ppm	30–100 ppm	4–100 ppm	<5 ppm
Collision energy	Low	Low	Low or High	Low
Analysis type	Targeted	Targeted/untargeted	Targeted/untargeted	Targeted/untargeted
Handling	Easy	Easy	Medium	Medium

possible, avoiding undesirable loss of analytes, and preventing the occurrence of random or systematic errors (Castro-Puyana et al., 2017; de Souza et al., 2019). When the targeted analysis is the selected analytical approach, sample preparation is a critical step since it should be highly efficient in the extraction of the targeted analytes under study while simultaneously allowing the reduction or elimination of possible interferent compounds from the matrix (Castro-Puyana et al., 2017; Lacalle-Bergeron et al., 2021; Niu et al., 2018; Pezzatti et al., 2020; de Souza et al., 2019). Therefore, the extraction method must be highly selective for the classes of the compounds to be analyzed. As shown in Tables 3 and 4, the most used extraction techniques are solid–liquid extraction (SLE) or liquid–liquid extraction (LLE), depending on the physical state of the sample, with the selectivity of the extraction being related to the extraction solvent used and its affinity with the analyte. The extraction can be achieved with one organic solvent, or alternatively, using consecutive extractions with several solvents of increasing polarity. To improve the efficiency of SLE, generally, vortex or ultrasonication is used (Lacalle-Bergeron et al., 2021; Patel et al., 2021; Žlabur et al., 2018). Other strategies may be needed, namely, filtrations, centrifugations, or a combination of both. Since botanical matrices are of great complexity due to their wide range of metabolites of different classes and with different physicochemical properties, selected solvents can also be used for the precipitation of interferents. In some cases, further cleanup steps may be necessary, for example, by solid-phase extraction with adequate sorbents to recover the target compounds with minimal matrix interferences (Koh et al., 2021b). The classical SLE and LLE methods are easy and cheap; however, they have the main disadvantage of frequently involving the use of large volumes of hazardous organic solvents. In recent years, new trends for green chemistry have been emerging and are expected to be increasingly applied also in the targeted analysis of PFS, namely, microextraction methods in which the volume of solvent needed is much lower (Spietelun et al., 2014; Žlabur et al., 2018). Liu et al. (2014) compared the performance of a matrix solid-phase dispersion (MSPD) method using silica as an adsorbent with heat-reflux and ultrasound-assisted extraction to extract 18 compounds from ginkgo, including flavonol glycosides, aglycones, and lactones. The results showed that the extraction efficiency was comparable, but MSPD presented the advantages of allowing the extraction and cleanup in a single run, requiring less time and solvents. Recently, different works have suggested the use of deep eutectic solvents (DES) as alternatives to conventional organic solvents for extracting phytochemicals from plant material and foods (Boateng, 2022; Wang et al., 2020). Although the use of such solvents is still very limited and mostly focused on the optimization of bioactive compound extraction, it is likely that their use will increase in the future for the extraction steps of different analytical methodologies as they are considered nontoxic, biodegradable, environmentally friendly, and inexpensive. Moreover, DES can be used in two-phase systems allowing the selective separation and extraction of compounds with differing polarities (Wang et al., 2020).

When the option of using a fingerprinting untargeted analysis is selected because of the lack of information about possible adulterants or identified markers, the technique of extraction should be able to extract as many groups of compounds as possible. For such an unspecific type of approaches, a nonselective extraction that can cover as many metabolites as possible is required. Since there is no universal chemical extraction method that covers all the classes of metabolites, the extraction procedure should be critically selected to provide a pool as representative as possible of the matrix complexity, which frequently means that the procedure should be kept as simple as possible. In the case of liquid samples, commonly, the sample is just filtered and, if necessary, diluted before being directly injected into the chromatographic system. Likewise, extracts can be resuspended in an adequate solvent

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TABLE 3 Application of targeted MS approaches to PFS authentication.

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
GC	Q-MS	nr	*Ephedra equisetina* and *Ephedra sinica*	Six ephedrine alkaloids	SLE with sonication	Three PFS (Ma Huang; capsules, tablets)	One PFS shows similar profile with the reference Ma Huang mixture, while the addition of artificial compounds is suggested for two products.	Hansen, 2001
	Q-MS	EI	37 plant species	Betulinic, oleanolic, ursolic, maslinic, and corosolic acids	SLE	38 plant extracts sold as PFS ingredients	Remarkable quantities of corosolic acid were found in *Lagerstroemia speciosa* and *Orthosiphon stamineus*, while oleanolic acid was abundant in *O. stamineus* and *Crataegus monogyna*; ursolic acid was identified in *O. stamineus*, *C. monogyna*, *L. speciosa*, and *Arctostaphylos uva-ursi*. Only *L. speciosa* was rich in maslinic acid. Minor amounts of betulinic acid were detected in *L. speciosa* and *C. monogyna* extracts.	Caligiani et al., 2013
	Q-MS	EI	*Ginkgo biloba*	Ginkgolic acids	SLE with sonication and centrifugation	21 PFS (capsules, tablets)	Samples with detectable amounts of ginkgolic acids showed a ratio of Δ10 to Δ8 isomers that were suggested to be from ginkgo leaves rather than seeds.	Wang, Zhao, et al., 2014
	Q-MS	EI	*Sedum roseum*	37 compounds including low-molecular-weight carbohydrates and phenylalkanoid glycosides	SLE	Eight PFS	Contents of rosarin were lower than rosavin and similar to rosin in the analyzed PFS. Only one PFS did not complied with a minimum of 3% rosavins and 0.8%–1.0% salidroside. Sedoheptulose was the most abundant carbohydrate. Coriose, 2,7-anhydro-D-altro-heptulopyranose, cellobiose, and gentiobiose were quantified for the first time.	Carrero-Carralero et al., 2018

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
LC	QQQ-MS/MS and Q-TOF-MS	ESI	Liliaceae plants including *Colchicum autumnale* and *Gloriosa superba*	Colchicine	SLE with sonication	26 *G. biloba* and *Echinacea* spp. PFS (capsules, caplets, tablets)	Colchicine was not detected in any PFS. LOD = 10 ng; LOQ = 20 ng.	Li et al., 2002
	Ion trap tandem MS	ESI	*Ginkgo biloba*	Aglycones (quercetin, kaempferol, and isorhamnetin) and flavonol glycosides (rutin and quercitrin)	SLE with sonication	Six PFS (tablets, soft and hard gelatin capsules)	Two samples presented quantifiable amounts of aglycones, yet at lower levels than flavonol glycosides.	Dubber et al., 2005
	Ion trap-MS	ESI	*Ginkgo biloba*	Ginkgolides A, B, and C and six flavonoids	SLE with sonication and centrifugation	Five PFS (capsules, tablets)	All samples revealed total flavonoid and terpene lactone contents according to the QC criteria. However, contents of each compound varied significantly.	Ding et al., 2006
	Ion trap-MS/MS	ESI	*Ginkgo biloba*	Ginkgolides A, B, and C, bilobalide, quercetin, quercetin-3-β-D-glucoside, quercitrin, kaempferol, isorhamnetin, and rutin	SLE with sonication, and centrifugation	Five PFS (capsules, tablets)	The sensitivity of different MS modes (full scan, SIM, SRM) was compared and SIM was selected for quantitation. All samples comply with the traditional quality control. However, MS analysis showed remarkable variations among products in the rutin and quercetin contents, suggesting fortification of two samples.	Ding et al., 2008
	TOF-MS	ESI	*Ginkgo biloba*	11 flavonol glycosides, three biflavones, and quercetin	SLE followed by sonication and centrifugation	16 PFS and six medicines	Four samples revealed distinct flavonol compositions when compared with the other medicinal and food products, and three of them were adulterated with quercetin.	Kakigi et al., 2012
	QQQ-tandem MS	ESI	*Ginkgo biloba*	Five lactones, 10 flavonol glycosides, and three aglycones	Matrix solid phase dispersion	12 PFS (tablets)	Flavonol glycosides, aglycones, and terpene trilactones were within 3.59–125.21, 0.031–22.31, and 3.45–57.8 μg/mg, respectively.	Liu et al., 2014

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Q-MS	ESI	*Ginkgo biloba*	Ginkgolides A, B, C, and J, and flavonoid aglycones (quercetin, kaempferol, isorhamnetin)	SLE and centrifugation	Six PFS (tablets, capsules)	Samples contain ginkgolides and flavonoids, but their contents are lower than the labeled values.	Demirezer et al., 2014
	Q-MS	APCI	*Ginkgo biloba*, *Sophora japonica*	Quercetin, kaempferol, isorhamnetin, and genistein	Sonication	Eight PFS (capsules, tablets)	Three samples, analyzed in unhydrolyzed form, exhibited high quercetin and kaempferol contents and low levels of isorhamnetin. Genistein was detected in these three products.	Wohlmuth et al., 2014
	Q-TOF-MS	ESI	*Sophora japonica* and *Ginkgo biloba*	Ginkgolides A, B, C, and J, bilobalide, flavonoids, and genistein	Sonication and centrifugation	25 PFS (capsules, tablets, liquids)	Eleven samples showed clear adulteration with *S. japonica* fruit or flower.	Avula et al., 2015a
	Orbitrap-MS	HESI	*Ginkgo biloba*	Flavonoids, free aglycones (quercetin, kaempferol, and isorhamnetin), genistin, and genistein	Sonication and centrifugation	14 PFS (tablets, caplets, capsules) and 15 powdered extracts	Four extracts were suggested to be adulterated due to the high levels of quercetin and kaempferol. Eleven PFS were adulterated mainly with rutin and/or the aglycones quercetin, kaempferol, and isorhamnetin. Genistein was found in three PFS, but at very low concentration.	Ma et al., 2016
	QQQ-MS/MS	APCI	*Ginkgo biloba*	Ginkgolides A, B, and C and bilobalide	SLE with sonication and LLE with ethyl acetate	11 PFS (capsules, tablets)	Three samples were considered authentic, with one being a high-quality PFS. The remaining eight showed different patterns, including no extract, addition of aglycones, and/or addition of other plant materials.	Czigle et al., 2018
	Q-MS	APCI	*Sophora japonica* and *Ginkgo biloba*	Genistein, sophoricoside, sophorabioside, genistin genistein, and cellobioside	SLE with sonication and acid digestion	22 PFS (tablets, capsules)	Eight samples indicated adulteration with *S. japonica* based on their isoflavone profiles.	Govindaraghavan, 2018

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Q-ion trap-MS	APCI, ESI	*Cimicifuga racemosa* (syn. *Actaea racemose*), other *Cimicifuga* species	Cimiracemates A and B; cimigenol-3-*O*-arabinoside, cimifugin, and cimifugin glucoside	SLE with sonication and filtration	Six drugs and 19 PFS	Species-specific markers allowed to differentiate *C. racemosa* from other *Cimicifuga* sp., both in raw materials and commercial PFS.	He et al., 2006
	Q-ion trap-MS	APCI	*Cimicifuga racemose*, other *Cimicifuga* species	Cimiracemoside and cimifugin	SLE with 0.5% NaOH and LLE with chloroform	11 PFS (capsules, tablets)	Three products were adulterated with cimifugin suggesting the presence of Asian *Cimicifuga* instead of black cohosh.	Jiang et al., 2006
	Q-TOF-MS	ESI	*Tanacetum parthenium*	Parthenolide	SLE and sonication	Three PFS (capsules, liquid) and seven plant samples	Parthenolide was detected in all samples, being the major chemical constituent of feverfew. LC–UV results were comparable to those of LC–MS. LC–MS was more sensitive than LC–UV. LOD = 0.3 μg/mL and LOQ = 0.5 μg/mL for LC–UV; LOD = 0.01 μg/mL for LC–MS.	Avula, Navarrete, et al., 2006
	Q-TOF-MS	ESI	*Hoodia gordonii*, *Opuntia ficus-indica*	P57	SLE, sonication and centrifugation	10 PFS (capsules, tablets)	P57 was not detected in four samples, suggesting a possible adulteration with *Opuntia ficus-indica*	Avula, Wang, et al., 2006
	Single-Q-MS	ESI	*Hoodia* species	12 hoodigosides including P57	SLE (solids) or LLE (liquids) with sonication and centrifugation	35 PFS (capsules, tablets, liquids)	LOD = 1 ng/mL by UPLC–MS and 300 ng/mL by UPLC–UV method. P57 was quantified in three samples, but it was <LOQ in five PFS; P57 was detected in one sample only by UPLC–MS. P57 was not detected in 26 samples.	Avula et al., 2008b
	Single-Q-MS	ESI	*Isodon japonicus* and *Isodon trichocarpus*	Diterpenoids (enmein, oridonin, eriocalyxin B)	SLE	Eight commercial products: one extract and seven herbal products	The isodonis extract and two samples of Isodonis Herba showed eriocalyxin B as the major compound, thus being originated from a distinct species such as *Isodon eriocalyx*.	Maruyama et al., 2007

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Single-Q-MS	ESI	*Caulophyllum thalictroides*	Eight triterpene saponins (cauloside A–D, H, and G; leonticin D; and saponin PE) and the alkaloid magnoflorine	SLE (capsules) or LLE (liquids) with sonication and centrifugation	Nine PFS (capsules and liquids) and two blue cohoshes	Magnoflorine, cauloside B–D and G, and leonticin D were identified in the nine PFS, with a significant variability in the amounts of triterpene saponins. Maximum daily intake of alkaloid and saponins varies with the form (solids/liquids).	Avula et al., 2011
	TOF-MS	ESI	*Petasites hybridus*, *P. frigidus*, and *P. vulgaris*	Four sesquiterpenoids (petasin, isopetasin, S-petasin, and 8β-H-eremophilanolide) and five pyrrolizidine alkaloids (seneciphylline *N*-oxide, integerrimine, senecionine, senecionine *N*-oxide, and senkirkine)	Solid PFS: SLE, sonication, centrifugation, and filtration. Liquid PFS: LLE and sonication.	21 PFS (capsules, soft gels)	Petasin, isopetasin, and 8β-H-eremophilanolide were the main compounds in all samples. Petasins were detected in *P. hybridus* and 15 PFS, but only showed contents according to their labels. Toxic pyrrolizidine alkaloids were detected in *P. hybridus*, *P. frigidus*, and seven PFS. HPLC–TOF-MS method was more sensitive (~5000 times) than UPLC–UV. LOD 5 and 0.1 μg/mL for pyrrolizidine alkaloids and sesquiterpenes, respectively, by UPLC–UV and 0.001 and 0.01 μg/mL, respectively, using HPLC–TOF-MS.	Avula, Wang, Wang, et al., 2012
	Single-Q-MS	ESI	*Passiflora* species	Five harman β-carboline alkaloids (harmalol, harmol, harmane, harmaline, and harmine) and four flavonoids (orientin, isoorientin, vitexin, and isovitexin)	SLE, sonication, centrifugation, and filtration.	Four PFS (capsules, liquids) and aerial parts of *Passiflora* species	All flavonoids were detected in *P. incarnata*, *P. edulis*, *P. violaceae*, and *P. morifolia*, and in three PFS samples. Harmane β-carboline alkaloids were not detected in any sample. LOD = 0.07–0.1 μg/mL.	Avula, Wang, Rumalla, et al., 2012

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	QTrap tandem-MS	ESI	79 plant species	98 compounds	SLE, sonication, centrifugation, and filtration.	104 PFS (powders, pills, tablets, capsules, liquids)	Ninety-eight biomarkers were screened to characterize 79 selected plants. Most PFS (55%) contained only botanicals; 45% also contained vitamins, minerals, and amino acids, among others. The proportions of botanicals varied a lot within 1%–100%. About 25% of PFS contained only a single plant, but some were mixtures of up to 12 botanicals, being 22% composed of at least six different ingredients. LOQ < 10 ng/mL for most compounds.	Mathon et al., 2013
	QQQ-MS	ESI	*Fangchi* spp. (*Sinomenium acutum*, *Stephania tetrandra*, *Cocculus trilobus*, and *Aristolochia fangchi*)	Magnoflorine, sinomenine, isosinomenine, syringaresinol, fangchinoline, aristolochic acid I, and tetrandrine	SLE with sonication	20 botanical raw materials	Magnoflorine and syringaresinol were identified for the first time in *S. tetrandra* and *C. trilobus*, respectively. The four species were differentiated based on the profile of marker compounds. LOD and LOQ values of the chemical markers were in the ranges of 0.01–0.05 μg/mL and 0.05–0.2 μg/mL, respectively.	Sim et al., 2013

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Q-TOF-MS	ESI	Chamomile (*Matricaria recutita* and *Anthemis nobilis*) and *Chrysanthemum morifolium*	Nine phenolic compounds [(*Z*)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid (*cis*-GMCA), chlorogenic acid, (*E*)-2-β-D-glucopyranosyloxy-4-methoxycinnamic acid (*trans*-GMCA), quercetagetin-7-*O*-β-D-glucopyranoside, luteolin-7-*O*-β-D-glucoside, apigenin-7-*O*-β-D-glucoside, chamaemeloside, apigenin 7-*O*-(6″-*O*-acetyl-β-D-glucopyranoside), apigenin] and one polyacetylene (tonghaosu)	Solid PFS: SLE, sonication, centrifugation, and filtration; Liquids: LLE and sonication	Seven PFS (capsules), 11 tea bags, and seven body and hair care products	*cis*-GMCA, *trans*-GMCA, apigenin-7-*O*-β-D-glucoside and tonghaosu were major constituents of German chamomile (*M. recutita*), while chamamaeloside and apigenin were main compounds Roman chamomile (*A. nobilis*) and luteolin-7-*O*-β-D-glucose the major compound of C. *morifolium* samples.	Avula et al., 2014
	Single Q-TOF-MS	ESI	*Citrus aurantium*, *Camellia sinensis*, and *Acacia rigidula*	Synephrine, oxilofrine, deterenol, yohimbine, rauwolscine, caffeine, and theophylline	Sonication, centrifugation, and filtration	Four PFS (tablets)	Synephrine, oxilofrine, deterenol, yohimbine, rauwolscine, caffeine, and theophylline were detected in the PFS. Two detected additional compounds were tentatively identified as β-methyl-β-phenylethylamines.	Venhuis et al., 2014
	Q-TOF-MS/MS	ESI	37 plant species of the Asteraceae, Boraginaceae, and Fabaceae families	25 pyrrolizidine alkaloids (PA)	Five tested methods; best results with sonication and centrifugation	Seven PFS (root extracts) and 37 plant samples	Senecionine and lycopsamine were found in the Asteraceae family samples, while lycopsamine and heliotrine were detected in the Boraginaceae family samples and senecionine and monocrotaline in the Fabaceae family. Five PFS showed the presence of PA. PA were identified in all samples.	Avula, Sagi, Wang, et al., 2015

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Trap-MS	ESI	*Vitis vinifera*, peanut, and pine	Gallic acid, catechin, epicatechin, and proanthocyanidins	Sonication and filtration	21 PFS of grape seed extracts (capsules)	Grape seed extract was not detected in 6 samples and were composed primarily of peanut skin extract. In 3 other samples, proanthocyanidins A-dimers suggest adulteration with peanut skin.	Villani et al. (2015)
	Single quadru-pole detector and TOF-MS	ESI	*Aegle marmelos*	Umbelliferone, scopoletin, marmesinin, 8-hydroxypsoralen, angelicin, aegeline, and marmelosin	Sonication, centrifuga-tion, and filtration	10 PFS (capsules) and 25 plant samples	UHPLC–PDA–MS determined simultaneously one alkaloid and six coumarins from *A. marmelos* and PFS. Marmelosin was the major compound in fruit samples. HPLC–TOF-MS analyzed aegeline enantiomers from plant and PFS samples. Aegeline: LOD = 0.1 μg/ mL; LOQ = 0.5 μg/ mL.	Avula, Chittiboyina, et al., 2016
	Q-TOF-MS	ESI	*Citrus paradisi* (grapefruit) and other *Citrus* species	18 flavonoids, three limonoids, and three synthetic preservatives	Sonication, centrifuga-tion, and filtration	17 PFS (capsules, tablets, liquids) and 15 citrus seed samples	Limonoids were the main secondary metabolites in all tested samples containing "inner seed only." Limonoids and flavonoids were detected in inner seed with outer seed coat and outer seed coat samples. Commercial grapefruit seed extracts and PFS contained more of flavonoids than limonoids. Two PFS contained a synthetic preservative (benzethonium chloride). LOD = 10–50 ng/mL	Avula, Sagi, et al., 2016
	Q-TOF-MS	ESI	*Rauwolfia serpentina* and *Rauwolfia vomitoria*	Ajmaline, yohimbine, corynanthine, ajmalicine, serpentine, serpentinine, and reserpine	Sonication, centrifuga-tion, and filtration.	21 PFS and seven plant samples	Samples showed wide variations in alkaloid contents. UHPLC–Q-TOF-MS/MS technique was applied in the characterization of alkaloids. LOD = 0.1–0.5 μg/mL; LOQ = 0.5–1.0 μg/mL	Sagi et al., 2016

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Ion trap MS/MS and Q-Orbitrap/MS	ESI, HESI	*Pueraria mirifica*	Miroestrol and isomiroestrol	Sonication, centrifugation, and filtration.	Eight PFS (tablets, pills, powder)	Miroestrol and isomiroestrol were detected in six PFS within 7.6–27.7 and 1.5–5.3 μg/g, respectively. LOD were 4.17 and 0.84 ng/mL for miroestrol and isomiroestrol, respectively; LOQ were 12.50 and 2.52 ng/mL, respectively.	Lee et al., 2017
	Q-TOF-MS	ESI	*Asimina* and *Annona* species	12 alkaloids and 23 acetogenins	Sonication, centrifugation, and filtration.	One PFS (capsule)	Thirty-five target compounds were characterized and detected from methanolic extracts of *Asimina* and *Annona* species based on the retention times and MS and MS/MS data. One PFS claiming to contain paw paw (*Asimina triloba*) showed a similar profile to twigs of *As. triloba*.	Avula et al., 2018
	Single-Q-MS	ESI	*Vangueria agrestis*	Geniposidic acid, neochlorogenic acid, chlorogenic acid, 2,4′,6-trihydroxy-4-methoxybenzophenone-2-*O*-β-D-glucoside, rutin, hyperoside, guaijaverin, and isochlorogenic acids A, B, and C	Sonication, centrifugation, and filtration.	17 PFS (capsules) and 19 plant samples	Phenolic compounds were found within 0.3–2.7 mg/dose in 12 PFS, but not detected in five. LOD = 0.025–0.1 μg/mL; LOQ = 0.1–0.25 μg/mL using UHPLC–PDA. LC/MS-ESI confirmed the identified compounds.	Avula et al., 2019
	Q-TOF-MS/MS	ESI	*Actaea racemosa*, *Actaea pachypoda*, *Actaea podocarpa*, *Actaea dahurica*, and *Actaea foetida*	Eight ester and four amide derivatives of hydroxycinnamic acids	Sonication, centrifugation, dilution, and filtration.	39 PFS (one NIST SRM3297, capsules, tablets, liquids), four plant samples (rhizome/root)	The use of four amide marker compounds made profile comparison easier and more efficient. PLS-DA was used to achieve maximum discrimination among classes.	Geng et al. 2019

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Q-TOF-MS	ESI	*Epimedium grandiflorum*, *Epimedium brevicornu*, and *Epimedium sagittatum*	15 prenylflavonoids	Sonication, centrifugation, and filtration; or microwave for some solid samples.	20 PFS (capsules, tablets, liquids) and 25 plant samples	PFS samples contained 8–15 prenylflavonoids and their contents suggest that they are of variable quality. Chemical profiling by LC–Q-TOF-MS combined with chemometrics discriminated among *Epimedium* species and PFS. LOD = 0.1–0.5 μg/mL; LOQ = 0.3–1 μg/mL.	Bae et al., 2020
	Single-Q-MS	ESI	*Tinospora crispa*, *Tinospora sinensis*, *Tinospora cordifólia*, and *Tinospora baenzigeri*	Magnoflorine, tinosineside A, borapetosides B, C, and F, (2*R*,5*R*,6*R*,8*R*,9*S*,10*S*,12*S*)-15,16-epoxy-2-hydroxy-6-*O*-(β-D-glucopyranosyl)-cleroda-3,13(16),14-trien-17,12-olid-18-oicacidmethyl ester, jatrorrhizine, *N-trans*-feruloyl tyramine, naringenin, and baenzigeride A	Sonication, centrifugation, and filtration	17 PFS (capsules, powder, and granules) and 17 plant samples	Borapetosides B, C, and F are good chemical markers for identifying *T. crispa* and distinguishing it from other *Tinospora* spp. Among *T. cordifolia* PFS, eight out of 10 agreed with the labeled species, but two were mislabeled: one contained tinosineside A, a marker for *T. sinensis*, and another contained borapetoside B. LOD = 0.3–10 μg/mL; LOQ = 1–30 μg/mL.	Parveen et al., 2020
	Q-TOF-MS	ESI	*Cissus quadrangularis*, *Cissus sicyoides*, *Cissus verticillata*, *Cissus aralioides*, *Cissus incisa*, *Cissus ulmifolia*, and *Cissus aristata*	Catechin, epicatechin, quercetin-3-*O*-β-glucopyranoside, kaempferol-3-*O*-β-glucoside, quercetin-3-*O*-β-rhamnoside, leachianol F, amurensin A, pallidol, resveratrol, and quadrangularin A	Sonication, centrifugation, and filtration.	19 PFS (capsules, tablets) and 24 plant samples	UHPLC–PDA quantified 10 compounds in *Cissus* spp. plant materials and PFS labeled with *C. quadrangularis*. Five PFS showed similar profile to *C. quadrangularis*, but all samples had highly variable contents. LC–Q-TOF-MS identified over 40 components in PFS.	Avula, Bae, Zhao, et al., 2021

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Single-Q-MS	ESI	*Moringa oleifera*	methyl-4-(α-L-rhamnopyranosyloxy) benzyl carbamate, niazirin, (+)-isolariciresinol-3a-*O*-β-D-glucopyranoside, rutin, isoquercitrin, quercetin-3-*O*-(6-*O*-malonyl)-β-D-glucopyranoside, lariciresinol-9-*O*-β-D-glucopyranoside, (+)-pinoresinol-4-*O*-β-D-glucopyranoside, and astragalin	Sonication, centrifugation, and filtration	13 PFS (capsules, powders)	Quantification of key compounds was achieved by HPLC–DAD, detecting 0.42–2.57 mg/100 mg of phytochemicals per PFS sample weight. All nine phenolic compounds varied among the PFS, with LOD of 0.2 μg/mL. Isoquercitrin and quercetin 3-*O*-(6-*O*-malonyl)-β-D-glucopyranoside are main compounds of *M. oleifera* leaves. LC/MS-ESI was used to characterize and confirm the compounds.	Fantoukh et al., 2021
	Single-Q-MS	ESI	*Citrus aurantium*	*p*-Synephrine, *p*-octopamine, and *p*-tyramine	Sonication, centrifugation, and further SPE.	12 PFS (preworkout; powders and gel capsules)	Five PFS showed trace amine ratios similar to that detected in the natural extracts of *C. aurantium* fruits. Synephrine was detected in four PFS, but with no detectable tyramine or octopamine, while the remainder had unusually high levels of octopamine. LOD = 0.136–0.246 μg/g; LOQ = 0.454–0.820 μg/g.	Koh et al., 2021b
	Single-Q-MS	ESI	*Citrus aurantium*	*R*-(−)-synephrine and *S*-(+)-synephrine	Sonication and extraction of a 1:5 dilution with aqueous ammonium acetate buffer (pH 7).	12 PFS (preworkout; powders and gel capsules)	Five PFS had enantiomeric ratios consistent with the reference materials (0.03–91.2 mg/g). Four had racemic ratios of synephrine (0.14–5.4 mg/g), two lacked any detectable levels of synephrine, and one had only the *S*-(+)-enantiomer (0.15 mg/g).	Koh et al., 2021a

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TABLE 3 (Continued)

Technique	Mass analyzer	Ion source	Target species	Chemical markers	Extraction	Products	Relevant information	Reference
	Single-Q-MS	ESI	*Cynara scolymus*	Sugars, phenolic acids, and flavonoid glycosides	SLE with sonication and centrifugation	20 PFS (capsules, tablets)	Most samples with composition similar to the reference extracts, but several PFS showed nontypical artichoke profiles, as determined by both GC–MS or HPLC–UV–MS methods. The multi-analytical strategy combined with chemometrics proved to be advantageous over single analytical techniques to detect multiple fraudulent practices.	Mena-García et al., 2021

Abbreviations: APCI, atmospheric pressure chemical ionization; DAD, diode-array detection; EI, electron ionization; ESI, electrospray ionization; GC, gas chromatography; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LLE, liquid–liquid extraction; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; PAD, photodiode array detection; PFS, plant food supplement; PLS-DA, partial least squares discriminant analysis; Q, quadrupole; SLE, solid-phase extraction; TOF, time-of-flight; UV, ultraviolet.

and directly analyzed. For solid samples such as plant powders, capsules, and tablets, the choice of the extraction solvent is a critical step. Since the extraction of metabolites with different polarities is limited by the use of a single solvent, mixtures of organic solvents and water are often considered because of recovering compounds with different polarities (Lacalle-Bergeron et al., 2021; Patel et al., 2021; Zhong et al., 2022). Moreover, strategies such as sonication, vortexing, or mechanical milling are also commonly adopted, aiming at increasing the extraction efficiency and recovery of a wide range of metabolites.

Although most works on the botanical authentication rely on the use of LC, in the few cases that may require GC–MS analysis, a derivatization reaction is usually carried out to convert target compounds into volatile analytes (Castro-Puyana et al., 2017; Lacalle-Bergeron et al., 2021; de Souza et al., 2019). In these cases, the derivatization process should be optimized, whenever possible, with the addition of reference standards to improve the reliability of the determinations (Patel et al., 2021).

3.2 | Targeted MS phytochemical analysis

Currently, prior knowledge about medicinal plants and their common bioactive compounds is often available when a phytochemical analysis for authenticity purposes is required. Factors such as the presence of specific plant metabolites, the variation and/or concentration range of each metabolite in different plant parts, as well as the existence of potentially toxic molecules characteristic of some species are widely reported in the literature, either in the form of research papers or as monographs (Ichim & Booker, 2021; Kellogg et al., 2019). Thus, either biomarkers or phytochemical profiles can be established aiming at targeted analysis (Simmler et al., 2018). The targeted approach has the advantage of providing the accurate identification and quantification of each selected compound, which can be a marker compound or a group of compounds comprising a profile. For that purpose, QQQ is frequently the choice due to its ability to reduce background noise, presenting high selectivity and sensitivity, thus allowing for an accurate quantitation (Dongen & Niessen, 2012; Holčapek et al., 2012). However, this type of analysis directly depends on the commercial availability of reference standards for the target compounds.

3.2.1 | Liquid chromatography

The use of biomarkers for assessing the botanical authenticity is one of the most straightforward approaches that can be applied either to raw materials, plant extracts, or

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TABLE 4 Application of untargeted MS approaches to PFS authentication.

Technique	Mass analyzer	Source	Species	Method of extraction	Statistical analysis	Samples	Relevant Information	References
GC	Triple Quadrupole	EI	*Matricaria chamomilla*, *Chamaemelum nobile*, and *Chrysanthemum morifolium*	Sonication and filtration	PCA and PLS-DA	27 authenticated plant samples, 35 herbal products (crude drugs, capsules, tea bags, powder, and extracts), 11 essential oils	A sample class prediction model was developed, demonstrating 100.0% accuracy for both recognition and prediction abilities. In general, the results were consistent with the labels. All samples from the United States were identified as German chamomile. Four products with few compounds were considered outliers probably due to age and storage conditions or to adulteration, requiring further analysis by other methods.	Wang, Avula, et al., 2014
	Q-MS	EI	*Cynara scolymus* cultivars: American Green Globe, French Hyrious, and Egyptian Baladi	PFS: SLE with sonication, and centrifugation Reference samples: SLE under stirring, and centrifugation	PCA	Bracts and leaf extracts (reference samples), 20 artichoke PFS, one milk thistle PFS	Most of the artichoke PFS presented a similar composition to reference extracts. Two samples showed a nontypical artichoke profile and were plotted apart based on their higher content of disaccharides and taxifolin.	Mena-García et al., 2021
	Q-MS	EI	*Cinnamomum cassia*, *C. verum*, *C. iners*, and *C. tamala*	SPME	PCA, HCA, OPLS-DA, and SIMCA	Five authenticated *Cinnamomum* sp. materials and four PFS (capsules)	A total of 126 peaks of cinnamon aroma compounds were obtained, where (*E*)-cinnamaldehyde was the major volatile. Dataset modeling associates two PFS to *C. cassia* due to their higher coumarin and low (*E*)-cinnamaldehyde contents.	Farag et al., 2022
LC	Q-TOF-MS	ESI	*Hypericum perforatum*	Sonication, centrifugation, and filtration; SPE on C18 cartridge of filtrate (500 μL), evaporation and redissolution.	PCA	Nine PFS (capsules, one tablet); two brands included two to three batches	PCA was able to discriminate between various preparations according to their global composition: three PFS had a different profile due to fatty acids, possibly used as additives. Samples were likely to be standardized for hypericins as they were reasonably constant.	Farag & Wessjohann, 2012
	Q-TOF-MS	ESI	*Cynara scolymus*	SLE with sonication, centrifugation, and filtration	PCA	Plant material of American Green Globe, French Hyrious, and Egyptian Baladi cultivars, seven PFS (capsules, tablets)	PCA discriminated the three cultivars mainly based on caffeic acid derivatives and scolymoside. PCA also differentiated between PFS of German and Egyptian origin; these last being more like French cultivar "Hyrious."	Farag et al., 2013

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TABLE 4 (Continued)

Technique	Mass analyzer	Source	Species	Method of extraction	Statistical analysis	Samples	Relevant Information	References
	Ion Trap MS/MS	ESI	*Ginkgo biloba*	SLE followed by sonication, centrifugation, and filtration.	Calculation of the correlative coefficient	15 plant samples (different locations in China), one commercial leaf sample, five PFS (tea, tablets, soft gel)	Similarity with authentic leaf samples was evaluated based on peak analysis and similarity analysis of MS fingerprints. A group of three samples of authentic leaves was distinct from the other group, possibly due to different growing conditions, plant age, or sex. A soft gel PFS showed low similarity with both groups of authentic ginkgoes; its high content of rutin suggests fortification.	Song et al., 2010
	Orbitrap-MS	ESI	*Ginkgo biloba*	Sonication followed by centrifugation and filtration.	PCA	16 plant materials and 16 dried leaf extracts (randomly adulterated), two SRM of leaves and dried leaf extracts	Score plots exhibited a trend with respect to the different adulteration levels (0%, 3%, 7%, and 12%) for dried leaf materials, both on positive and negative modes. Ginkgo extract samples did not obtain initial separations based on adulteration level, but score plots separated the adulterated samples from the nonadulterated ones.	Cruz et al., 2020
	Q-TOF-MS	ESI	*P. ginseng*, *P. notoginseng*, and *P. quinquefolius*	SLE with sonication, and centrifugation.	PCA	Four authentic roots, two PFS	PCA analysis discriminated among the three ginseng species and confirmed the correct labeling of the commercial products. Ten main compounds were identified and considered as potential markers for the three species.	Yuk et al., 2016
	Q-TOF-MS	ESI and APCI	*Hippophae rhamnoides*	Nonpolar fraction: oil evaporated to dryness, and redissolved. Polar fraction: LLE	Not performed	Sea buckthorn and sunflower oils (reference samples), one PFS (oil capsules)	Monoacylglycerols, diacylglycerols, triacylglycerols, and free fatty acids profiles, and the absence of polar monogalactosyl diacylglycerols in the PFS and in sunflower oil confirmed the adulteration.	Hurkova et al., 2017
	Q-TOF-MS/MS	ESI	*Asimina* and *Annona* species	Sonication, centrifugation, and filtration.	Not performed	Authenticated plant material (*As. triloba*, *As. parviflora; An. squamosa*, *An. muricata*, and *An. x atemoya*), one PFS	Ninety-six nontargeted compounds were identified based on accurate mass. One PFS claiming to contain paw paw (*Asimina triloba*) showed a similar profile to twigs of *As. triloba*.	Avula et al., 2018

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TABLE 4 (Continued)

Technique	Mass analyzer	Source	Species	Method of extraction	Statistical analysis	Samples	Relevant Information	References
	Q- Orbitrap-MS/MS	ESI	*Hydrastis canadensis*, *Coptis chinensis*, *Mahonia aquifolium*, and *Berberis vulgaris*	SLE, filtration	PCA	35 goldenseal PFS (capsules, tinctures, powdered bulk materials, bagged teas); reference plant samples of *H. canadensis*, C. *chinensis*, *M. aquifolium*, and *B. vulgaris*	Commercial samples clustered with authenticated goldenseal reference counterparts, except for three PFS. These were closely clustered to reference samples of adulterants, suggesting their formulation as *B. vulgaris*, *C. chinensis*, and *M. aquifolium*, respectively, or a mixture of plants.	Wallace et al., 2018
	Q-Orbitrap-MS	HESI	*H. canadensis*, *C. chinensis*	SLE	PCA and composite score analysis (unsuper-vised) and SIMCA (supervised)	10 goldenseal PFS (capsules); reference plant samples of *H. canadensis* and *C. chinensis*	Training set composed of *H. canadensis* adulterated with known quantities (5%–95%) of *C. chinensis*. SIMCA provided the greatest discrimination potential to detect adulteration.	Wallace et al., 2020
	Q-TOF-MS/MS	ESI	*Vangueria agrestis*	Sonication followed by centrifugation and filtration	PLS-DA	Six authentic samples of *V. agrestis*, seven PFS	Chemometrics was used to visualize the differences between root and aerial parts and to identify potential chemical markers that differentiate among different parts of *V. agrestis* samples and PFS. All PFS showed to contain *V. agrestis* stem extract, confirming this claim in two of them.	Avula et al., 2020
	Q-TOF-MS	ESI	*Epimedium grandiflorum*, *E. brevicornu*, and *E. sagittatum*	Liquid samples: sonication, centrifugation, and filtration. Solids: sonication, centrifugation, and filtration or microwave extraction	PCA	20 PFS (capsules, tablets, liquids) and 25 plant samples	PCA was able to differentiate among the three studied *Epimedium* species.	Bae et al., 2020
	Q-TOF-MS	ESI	*Stephania tetrandra*, *Aristolochia fangchi*	SLE with sonication, followed by SPE to obtain five fractions	Not performed	One raw material	A comprehensive phytochemical fingerprint comprising 393 isoquinolines of *S. tetrandra* was obtained. The absence of aristolochic acid-related mass signals confirmed the authentication of *S. tetrandra*.	Chen et al., 2020

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TABLE 4 (Continued)

Technique	Mass analyzer	Source	Species	Method of extraction	Statistical analysis	Samples	Relevant Information	References
	Q-TOF-MS/MS	ESI	*Bulbine natalensis* and *Bulbine frutescens*	Sonication, centrifugation, and filtration	PCA, PLS-DA	Three authenticated plant samples (*B. natalensis* and *B. frutescens*), nine PFS	Fifty-five anthraquinone-type compounds, including 11 standard compounds, were identified in the crude extracts of two *Bulbine* species. Based on chemometrics, five PFS showed similar profiles to *B. natalensis* stem, while four did not.	Avula, Bae, Wang, et al., 2021
DART-HRMS	TOF-MS	DART	*Angelica tenuissima*, *A. gigas*, *A. dahurica*, and *Cnidium officinale*	Not applicable	OPLS-DA	10 roots of each species	Characteristic fingerprints were obtained for each species. From the loading plots, compounds were identified as important chemical markers for the different species.	Lee et al., 2012
	Q-TOF-MS	SVP	*Hippophae rhamnoides*	Nonpolar fraction: dilution in toluene Polar fraction: LLE	Not performed	Sea buckthorn and sunflower oils (reference samples); one PFS (sea buckthorn oil-based capsules)	The oil supplement presented a profile similar to that of sunflower, confirming its adulteration.	Hurkova et al., 2017
	QOrbitrap-MS	SVP	Radix Angelicae and Rhizoma Corydalis	SLE with sonication	PCA, PLS-DA	Five PFS (Yuanhu Zhitong tablets of different manufacturers)	Two samples showed differences in ion intensities, suggesting their different chemical components. The separation into three groups illustrated the quality differences among the samples. Different analytical markers were identified beyond the conventional tetrahydropalmatine. The method was fast in sample preparation and analysis.	Li, Liu, et al., 2017
FI	Iontrap-MS	ESI	*Scutellaria lateriflora*, *Teucrium canadense*, and *T. chamaedrys*	SLE with sonication	PCA	Four authenticated aerial parts of *S. lateriflora*, 15 PFS (*S. lateriflora* and Chinese skullcap).	The method is simple and fast, allowing identification of contamination with *T. canadense* and adulteration. Five PFS were confirmed as authentic, while one was contained *Scutellaria baicalensis*, three very low in *S. lateriflora*, and four used *T. canadensis* that could be harmful to consumers.	Sun & Chen, 2011

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TABLE 4 (Continued)

Technique	Mass analyzer	Source	Species	Method of extraction	Statistical analysis	Samples	Relevant Information	References
	Iontrap-MS	ESI	*Panax ginseng*, *P. quinquefolius*, and *P. notoginseng*	SLE with sonication	PCA, SIMCA, PLS-DA, FuRES	44 *P. quinquefolius*, 12 *P. ginseng*, and four *P. notoginseng* samples	The three species were well separated in the PCA plot. Supervised PLS-DA and FuRES were excellent classification methods for identifying the three *Panax* species.	Chen et al., 2011
	Iontrap-MS		*P. ginseng* and *P. quinquefolius*	SLE with sonication, centrifugation	SIMCA, FOAM, PLS-DA, FuRES	44 *P. quinquefolius* and eight *P. ginseng* samples and their mixtures (90%, 80%, and 50% of *P. quinquefolius*)	All classification and modeling methods discriminated between 100% *P. quinquefolius* and 100% *P. ginseng*. The modeling methods performed better as they were able to identify the adulterated samples.	Harnly et al., 2013
	Q-MS	ESI	*Actaea racemosa*, *Actaea pachypoda*, *Actaea podocarpa*, *Actaea cimicifuga*, and *Actaea rubra*	SLE with sonication	SIMCA, FOAM, PLS-DA, FuRES	91 *Actea* spp. root materials, 14 commercial roots, and 14 PFS (tablets, capsules, liquids)	FIMS was able to discriminate among the five species when raw materials are used. None of the tested commercial roots were from *A. racemosa*. For PFS, FIMS indicated that commercial samples were not similar to any of the raw *Actaea* materials, suggesting that preparation produced significantly different metabolic profiles that impacted the chemical fingerprints.	Harnly et al., 2016
	Iontrap-MS	ESI	*Echinacea purpurea*	SLE with sonication	PCA, F-test spectrum	16 authenticated *E. purpurea* aerial parts, 19 PFS (capsules, tablets, liquids)	*Echinacea purpurea* was identified in five out of six single-ingredient PFS and seven out 13 mixed or unknown species PFS.	Harnly et al., 2017

Abbreviations: APCI, atmospheric pressure chemical ionization; DART, direct analysis in real-time; EI, electron ionization; ESI, electrospray ionization; FIMS, flow-injection mass spectrometry; FOAM, fuzzy optimal associative memories systems; FuRES, fuzzy rule-building expert system; GC, gas chromatography; HRMS, high-resolution mass spectrometry; LLE, liquid–liquid extraction; MS, mass spectrometry; OPLS, orthogonal partial-least squares; PCA, principal component analysis; PFS, plant food supplement; PLS-DA, partial least squares discriminant analysis; Q, quadrupole; SIMCA, soft independent modeling of class analogy; SLE, solid-phase extraction; SPME, solid-phase microextraction; TOF, time-of-flight.

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PFS. Ideally, if a marker compound for a potential adulterant species is known, its detection in the analyzed product (plant, extract, or PFS) would reveal the presence of the adulterant. With this aim, the aristolochic acid has been proposed to identify the presence of *Aristolochia fangchi* in the traditional Chinese herbal medicine "fangchi," which comprises the rhizome of *Sinomenium acutum* and the radix of *Stephania tetrandra* (Sim et al., 2013). In this case, the chemical composition differs significantly among the three species, with *A. fangchi* being the only one containing aristolochic acid, a nephrotoxic and carcinogenic compound, which can be used as a marker for its inadvertent addition to *S. tetrandra* or *S. acutum*. The detection of adulterant plants based on characteristic markers was also proposed for black cohosh (*Actaea racemosa* L., syn. *Cimicifuga racemosa* L.), an herb native to North America commonly used in PFS for the treatment of symptoms related to menopause. Actein, 23-epi-26-deoxyactein, acetylshengmanol-3-*O*-xyloside, cimigenol-3-*O*-arabinoside, and cimigenol-3-*O*-xyloside have been reported as the major triterpene glycosides found in black cohosh, though several of them can also be found in other species of the same genus and, thus, cannot be used by their own as authenticity markers of *A. racemosa*. However, different authors have proposed the use of the furanochromones, cimifugin and cimifugin-3-*O*-glucoside, as reliable markers of *A. racemosa* adulteration with other *Actea* species due to their absence in black cohosh while existing in these species (He et al., 2006; Jiang et al., 2006). Jiang et al. (2006) developed a simple approach based on a positive mode APCI LC–MS approach using selected ion monitoring (SIM) mode to simultaneously scan the characteristic ions of cimifugin (*m/z* 307), cimifugin glycoside (*m/z* 469), and cimiracemoside C (*m/z* 621), the last as it had previously been described as a characteristic compound of black cohosh (He et al., 2000). The method allowed the differentiation of black cohosh from three Asian *Actaea* species (*A. cimicifuga*, *A. dahurica*, and *A. yunnanensis*) and the identification of four commercial products adulterated with the addition of Asian *Actea* species. Later, He et al. (2006) studied 10 *Actea* species, including seven Asian and two American in addition to *A. racemosa*, and confirmed cimifugin and its glycoside as adulteration markers. In addition to these two markers, the authors suggested the simultaneous determination of cimigenol-3-*O*-arabinoside as a characteristic marker of black cohosh (*A. racemosa*) because, apart from *Cimicifuga rubifolia*, it was absent in the other eight evaluated species. Three out of four analyzed commercial samples were consistent with the presence of *A. racemose*, while one was identified as *Cimicifuga foetida* due to the presence of cimicifugoside H-1, which was shown to be present only in this species.

Lee et al. (2017) developed LC–Q-Orbitrap/MS and LC–MS/MS methods for the qualitative and quantitative detection of miroestrol and isomiroestrol, respectively, as markers of PFS adulteration with *Pueraria mirifica* (syn. *Pueraria candollei* var. *mirifica* [Airy Shaw & Suvat.] Niyomdham). This plant, also known as white Kwao Krua, is used in Thai traditional medicine due to its phytoestrogen compounds, being present in products advertised as having rejuvenating and breast enhancement effects. Miroestrol has been demonstrated to be a potent phytoestrogen and is only found in *P. candollei*, thus being a suitable marker of this species.

Genistein was suggested as a marker compound for detecting the adulteration of ginkgo extracts added with *S. japonicum*, despite some controversy on the presence/absence of this isoflavone in *G. biloba*. According to some authors that evaluated different samples of ginkgo, including leaves, seeds, stems, and fruits, isoflavones are not naturally produced by this species (Avula, Sagi, Gafner, et al., 2015; Wohlmuth et al., 2014). However, some contradictory studies have reported the presence of genistein in ginkgo, albeit in very low concentrations (Yao et al., 2017) and not evenly distributed because it was found in the stems, fruits, and leaves of older male trees, while it was absent in the leaves of younger male and female trees (Pandey et al., 2014). Moreover, the levels seem to display some seasonal variability, being lower in May and June and higher in September (Yao et al., 2017). Despite its possible presence in ginkgo, the levels of genistein would be very low and, thus, its use as a marker of adulteration should not be excluded considering the high concentration of isoflavones that naturally exist in the adulterant *S. japonica*. The applicability of this marker was demonstrated in the study of Govindaraghavan (2018) when evaluating 22 commercial samples acquired in Europe, Australia, and New Zealand, all declared as mono-herbal formulations (containing only *G. biloba* leaf extract as the claimed active ingredient). While 14 samples showed the absence or vestigial amounts (<0.25% w/w) of this compound, in the other eight samples, the contents ranged from 1.72% to 9.56%, clearly demonstrating fraudulent practices. To confirm this hypothesis, the isoflavone composition was assessed by HPLC–DAD–MS showing the presence of genistein, sophoricoside, sophorabioside, genistin, and genistein cellobioside in the samples suspected of adulteration, a composition identical to that of found in *S. japonica*. Therefore, it can be concluded that high levels of genistein can be used as a marker of ginkgo's adulteration with *S. japonica*. Selecting a specific chemical marker that is present in high amounts in the plant is particularly advantageous for samples consisting of plant mixtures, as most PFS, and/or when a small amount of adulterant is mixed in the product. When the selected marker is

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naturally present in small amounts, its detection can become unfeasible if the plant is a minor ingredient of the product formulation.

The use of the oxypregnane steroidal glycoside P57, the only reported active constituent from *Hoodia gordonii* that acts as an appetite suppressant, has been suggested as a marker of this species (Avula et al., 2006b; Avula et al., 2008a), together with three other species of the same genus that also showed to contain this compound (*Hoodia ruschii*, *Hoodia currorii*, and *Hoodia parviflora*). Unlike raw plant material, in PFS for weight loss, *H. gordonii* is frequently used mixed with other botanicals (green tea, cocoa, green coffee, guarana, *Panax ginseng*, yerba mate, ginger root, etc.) and, among the four *Hoodia* species, *H. gordonii* exhibited the lowest concentration of P57 (0.043%) (Avula et al., 2008a). The analysis of 35 commercial PFS by UPLC–UV–MS enabled the detection and quantification of P57 based on UV absorption in nine products. Of those, four showed to be under the limit of quantification, while in one P57 was only detected by MS, demonstrating the superior sensitivity of MS compared with UV detection (Avula et al., 2008b). Nevertheless, these results should be analyzed with caution, considering the naturally low content of the marker compound and the lack of information about the product's detailed formulation (concerning the quantity of plant or extract used); the nondetection of P57 may not be sufficient to consider those samples as being adulterated.

Besides allowing for the detection of certain adulterants, specific biomarkers can be used in targeted approaches for species authentication to confirm the botanical origin in single- or mixed-species products. With this purpose, one of the most studied species is *Ginkgo biloba* (Table 3), owing to its popularity and high market demand, making it vulnerable to economically motivated adulterations (Grazina, Amaral, & Mafra, 2020; Grazina, Amaral, Costa, et al., 2020; Market.us, 2019). This plant is widely used for its capacity to ameliorate the cognitive loss in the elderly and improve minor peripheral circulatory illnesses due to their contents in two major groups of compounds, namely, terpenes and flavonoids (Diamond & Bailey, 2013; EMA, 2015a, EMA, 2015b; Singh et al., 2008; Suliman et al., 2016). The terpene trilactones bilobide and gingkolides are unique to this species and, thus, they can be effectively used as *G. biloba* markers. Since they do not absorb in the UV range and other absorbing compounds present in the matrices may interfere with their detection, their identification relies mainly on MS detection (Avula, Sagi, Gafner, et al., 2015; Demirezer et al., 2014). Accordingly, Avula et al. (2009) developed two methodologies based on the use of different techniques, namely, an LC/ESI-TOF-MS operating in the positive ion mode with extractive ion monitoring and a UPLC–MS in positive mode with SIM to quantify five characteristic terpene lactones (bilobalide and gingkolides A, B, C, and J). As marker compounds, their absence indicates the complete substitution of the plant material or extract with another species. Nonetheless, further information is required to identify cases of partial substitution of *G. biloba* with other species. To that end, the identification and quantification of a group of selected compounds and the comparison of results with a characteristic profile are one of the most suitable approaches. Targeted profiling of flavonoids and terpenes has been widely used for assessing the authenticity of ginkgo dry extracts or products thereof for which there are guidelines. According to the European Pharmacopoeia (2008), the standardized *G. biloba* extract should contain 22%–27% flavonoids, 2.6%–3.2% bilobalide, 2.8%–3.4% ginkgolides, and a maximum of 5 ppm of ginkgolic acids. The pharmaceutically prepared dry extract and most frequently used as phytomedicine is standardized to contain 24% of ginkgo flavonol glycosides and 6% terpene lactones, similar to the proprietary extract EGb761® used in several clinical studies (American Botanical Council, 2000). To calculate the proportion of flavonoids, the pharmacopoeia preconizes a simple assay based on the use of HPLC–UV after acid hydrolysis of the extract. With this step, the flavonoid glycosides are hydrolyzed and then quantified by HPLC–UV as three major aglycones, namely, quercetin, kaempferol, and isorhamnetin. This approach greatly simplifies the separation and analysis of compounds, although it has been criticized because it cannot differentiate frauds carried out by aglycone fortification to meet the required percentage of flavonols. To overcome this gap, the United States Pharmacopoeia (USP) introduced limits for the ratios of aglycones, with the ratio of the kaempferol to the quercetin peak areas being no less than (NLT) 0.7 and isorhamnetin to quercetin NLT 0.1. (USP, 2014a). Nevertheless, analyzing the profile of flavonols, before and after hydrolysis, Wohlmuth et al. (2014) demonstrated that samples adulterated with the addition of pure flavonols could comply with these criteria and remain without being detected. Later, limits for the two compounds most prone to be added as adulterants, namely, rutin and quercetin, were introduced (no more than 4% and 0.5%, respectively) as another means to detect the adulteration of ginkgo extract by the addition of pure flavonols or flavonol-rich extracts (Avula, Sagi, Gafner, et al., 2015; USP, 2014b). However, since in the classical UV-based methodology no structural identification of the compounds is achieved and their individual contents can vary with many factors (climate, soil, plant part, plant genetics, etc.), different works based on the profiling of ginkgo compounds have been carried as more reliable and accurate methodologies for the authentication of *G. biloba*. Ding et al. (2006) proposed, for the first time,

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the simultaneous quantification of 10 compounds from the two major groups of constituents in ginkgo, namely, bilobalide, ginkgolides A, B, and C, quercetin, kaempferol, isorhamnetin, rutin, quercetin-3-glucoside, and quercitrin, by HPLC–ESI-MS. The sensitivity of the method was tested in full scan, SIM, and selected reaction monitoring with a better limit of detection (LOD) being achieved in SIM. The method was applied to five commercial products and compared with the classical UV approach. While all the samples were in good agreement with the QC value of 24% for total flavonoids using the classical acid hydrolysis UV method, much lower values were obtained with the newly developed MS method. These lower values are explained by the fact that only three flavonol glycosides and three aglycones were considered in the methodology, while many more flavonoids exist in the plant. Nevertheless, the method demonstrated its superiority in terms of authenticity purposes because it was able to identify a sample potentially adulterated by the addition of quercetin since a content of 7.98% was found and this aglycone is present in the plant only in minor amounts. Later, Liu et al. (2016) developed an improved approach using UPLC tandem-triple-quadrupole (QQQ)-MS, allowing the simultaneous identification and quantification of the same five terpene lactones and three aglycones, but increasing the number of flavonol glycosides to 10 different compounds. The usefulness of ginkgo's terpene lactones was also demonstrated by Demirezer et al. (2014) who, in addition to the classical determination of the three aglycones, proposed the quantification of four ginkgolides (A, B, C, and J) by LC–MS. Those authors verified that the contents determined in THMP and PFS were in general lower than those declared on the products' labels, especially in PFS for which five samples showed much lower contents of ginkgolides. A high level of adulteration was also reported by Avula, Sagi, Gafner, et al. (2015), both due to the addition of pure flavonoids or flavonoid-rich plant extracts, such as *S. japonica*. The screening of chemical profiles by UHPLC–LC–DAD–QTOF-MS and the use of *G. biloba* and *S. japonicum* representative compounds, confirmed by their retention time, accurate mass, and MS/MS spectra, allowed the unequivocal discrimination of the authentic from the adulterated PFS. The identification of high levels of compounds, such as rutin, quercetin, genistein, and sophorabioside (the main compound in *S. japonicum*), when compared with authentic ginkgo material, enabled the detection of adulterations with *S. japonicum* fruits in 44% of the PFS. Furthermore, eight PFS showed amounts of quercetin, kaempferol, and isorhamnetin that suggested adulteration with synthetic aglycones (Avula, Sagi, Gafner, et al., 2015). Kakigi et al. (2012) used a similar targeted analysis based on profiling 15 compounds (11 flavonol glycosides, three biflavones, and quercetin) by UHPLC–UV–TOF-MS. However, the approach was slightly different since it did not comprise full quantification of the compounds. The areas obtained for six ginkgo medicines and 16 ginkgo food products were submitted to principal components analysis (PCA), generating four different groups. All six medicinal products were joined in the same group, together with seven ginkgo food products based on their high flavonol glycoside contents, demonstrating their similar origin. The food products were discriminated against due to the high contents of biflavones or an aglycone.

MS hyphenated with HPLC or UHPLC has also been proposed to confirm the identity of targeted compounds together with their quantification using other detectors. Avula et al. (2011) developed an LC–UV–evaporative light scattering detector (ELSD)–MS methodology to determine a major alkaloid (magnoflorine) and eight triterpene saponins in the roots of *Caulophyllum thalictroides* (L.) Michx. (blue cohosh) and PFS claiming to contain blue cohosh as a single botanical ingredient. ESI-MS data in the positive mode allowed us to identify and confirm magnoflorine and five saponins in all the nine analyzed PFS, suggesting the presence of blue cohosh, despite the absence of some saponins. Moreover, the results demonstrated a great variability of total saponins among commercial products (Avula et al., 2011).

A simple and fast UHPLC–DAD–MS method was developed by Avula, Chittiboyina, et al. (2016) for the detection of aegeline, the major alkaloid in leaves and fruits of *Aegle marmelos* (wood apple), together with six coumarins in PFS claiming to contain aegeline. The compounds were quantified based on UV detection and their identity was confirmed by MS. In addition, a chiral HPLC–TOF-MS method was developed to resolve aegeline enantiomers, which showed the prevalence of the S-enantiomer in the natural samples, while both enantiomers were present in similar amounts in the PFS, suggesting the synthetic origin of the compound (Avula, Chittiboyina, et al., 2016). The use of enantiomeric ratios was also suggested by Koh et al. (2021a) to authenticate *Citrus aurantium* supplements based on synephrine enantiomers since the R form predominates in natural samples, while the synthetic compounds are often racemic mixtures. The use of MS detection in line with UV/Vis or DAD detectors for the identity confirmation of target compounds was also reported for the determination of nine phenolic compounds in *Moringa oleifera* leaves and PFS (Fantoukh et al., 2021), for the identification of three biogenic amines in *Citrus aurantium* preworkout supplements (Koh et al., 2021b), and for the differentiation of *Tinospora* species based on 10 compounds, including six specific chemical markers (4 furanoditerpenoids characteristic of *T. crispa*, baenzigeride A of *T. baenzigeri*, and tinosineside A of *T. sinensis*) (Parveen et al., 2020).

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3.2.2 | Gas chromatography

The first chromatographic technique to be combined with MS was GC–MS, which is still widely accepted as a powerful technique to analyze small volatile molecules. Furthermore, it is one of the most useful analytical tools for the analysis of complex matrices, including metabolites of natural sources with volatile and semivolatile properties, due to its high separation capacity and capability of detection and quantification of compounds at trace levels (Kaklamanos et al., 2020; Pandohee et al., 2023; Pferschy-Wenzig & Bauer, 2015; Simmler et al., 2016; Sparkman et al., 2011; Wadood et al., 2020). Despite its advantages, the application of GC–MS is limited due to the thermal instability of some metabolites and the nonvolatility of several phytochemicals (Theodoridis et al., 2011; Tistaert et al., 2011). Hence, LC–MS systems have been the preferred approach in the evaluation of botanicals, extracts, and PFS (Table 3).

Hansen (2001) developed a GC–MS approach to evaluate the authenticity of three PFS containing the Chinese herb Ma Huang, a mixture of *Ephedra equisetina* Bunge and *E. sinica* Stapf, based on the profile of ephedrine alkaloids. The results suggested that one product might be augmented by L-ephedrine, while another is a synthetic mixture with high contents of caffeine (Hansen, 2001). Wang, Zhao, et al. (2014) developed and validated a GC–MS method operating in SIM mode for the quantitative analysis of trimethylsulfonium hydroxide-derivatized ginkgolic acids in plant materials, extracts, and commercial PFS. The technique was advantageous over LC methods because it was able to resolve the double bound positional isomers of ginkgolic acids, allowing to distinguish different plant parts. The isomer ratio displayed by all the analyzed PFS that contained detectable amounts of Δ8 and Δ10 isomers of the C15:1 ginkgolic acid esters indicated that they all originated from *G. biloba* leaves and not seeds or sarcotesta.

Besides single and triple quadrupole analyzers due to their high sensitivity, resolution power, fast analysis, and multitarget detection, TOF is frequently coupled to GC due to its high suitability for performing phytochemical fingerprinting based on accurate mass measures (Carrasco-Pancorbo et al., 2009). Carrero-Carralero et al. (2018) developed a GC–MS and a GC×GC–TOF-MS to simultaneously analyze low-molecular-weight carbohydrates and phenylalkanoid glycosides in *Rhodiola rosea* roots and PFS, after a derivatization step. The use of comprehensive bidimensional chromatography allowed the tentative identification of a much higher number of compounds (total of 85), while the quantitative determination of 37 compounds was achieved by GC–MS in SIM mode. Differences in rosavin compounds were observed among the eight PFS evaluated; nonetheless, except for one sample, the extracts presented >3% of rosavins and between 0.8% and 1.0% of salidroside as generally used in standardized extracts for preclinical and clinical studies (Carrero-Carralero et al., 2018).

Recently, Mena-García et al. (2021) suggested a multi-analytical strategy encompassing the use of GC–MS and HPLC–UV–MS combined with chemometrics for the authenticity assessment of artichoke-containing PFS for overweight control. Different bract and leaf extracts were used as reference samples, and both methods were applied to 21 commercial products. For GC–MS analysis, the artichoke extracts were derivatized to trimethylsilyl oximes allowing to detect *chiro*-, *scyllo*-, and *myo*-inositols in all reference samples and commercial products, except for one. The absence of these compounds previously reported as characteristic of artichoke leaf and bract extracts raised doubts about the botanical origin of the sample. Multivariate analysis of the GC–MS results highlighted two samples as possible frauds due to their higher contents of disaccharides and taxifolin. However, when data from both methods were considered, a group of artichoke PFS was also evidenced as having better quality, showing that the combination of different tools can be advantageous.

3.2.3 | Other hyphenated MS-targeted approaches

Although LC and GC are the techniques most commonly hyphenated with MS and the most applied in targeted analysis, others such as supercritical fluid chromatography (SFC) and NMR can also be combined with MS (Table 3). SFC is a chromatographic variant that uses supercritical fluids (SFs) as mobile phase. SFs are characterized by low viscosities, presenting improved diffusion ability. These properties, in addition to the pressure and temperature above their critical point, allow them to behave as substance transporters such as in GC and, at the same time, can dissolve those compounds, similarly to LC (Herrero et al., 2006; Taylor, 2009). Currently, carbon dioxide is the SF most used as the mobile phase, leading to enhanced sensitivity and robustness (West, 2018). Wang et al. (2016) developed an SFC–MS-based approach for the authenticity assessment of ginkgo-containing PFS by analyzing the terpene lactones and ginkgolic acids. The results showed high variability of total terpene lactones, and three out of eight PFS showed ginkgolic acids above the legislation maximum limit of 5 ppm. Only 25% of the samples presented contents of terpene lactones in the advisable range of 5%–7%, while 62.5% were below 5%, and 12.5% were above 5%. Jones et al. (2014) proposed a similar system (SFC–PDA–Q-MS) to analyze and discriminate Roman chamomile (*Chamaemelum*

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nobile) and German chamomile (*Matricaria chamomilla*, syn. *Chamomilla recutita*) extracts based on 11 chemical markers. The method was applied to 11 commercial chamomile infusions showing that they all contained German chamomile. Compared with a general UHPLC method, the SFC allowed a better separation of isobaric compounds and proved to be an efficient tool to separate sesquiterpene lactones from chamomile extracts (Jones et al., 2014).

3.3 | Untargeted MS phytochemical analysis

In contrast with targeted strategies, untargeted MS approaches are considered unbiased as they aim at providing as much information as possible by comprehensively measuring unspecified compounds present in a sample, resulting in a fingerprint (Gibbons et al., 2015; Simmler et al., 2018). This metabolic or phytochemical fingerprint is not intended for the identification of the entire set of detected compounds, but rather for pattern comparison, generally using chemometric approaches. Since HRMS is undoubtedly the most used technique in untargeted approaches, with modern hybrid MS analyzers allowing the simultaneous full scan and MS/MS or MS^n acquisition in a single run, very large datasets are obtained. Therefore, data processing and potent multivariate analysis to reduce the complexity of the data and explore possible correlations are generally required, with the consequent need for advanced statistical analysis skills when attempting untargeted analyses. Detailed information regarding data processing steps (such as peak picking and deconvolution, alignment, and gap filling) and corresponding tools, as well as on the use of supervised or unsupervised statistical analyzes in untargeted metabolomics for food authentication and/or investigation of food biomarkers, can be consulted in recent reviews (Lacalle-Bergeron et al., 2021; Zhong et al., 2022). Untargeted metabolomics can also be applied as a first step toward the development of targeted approaches. Once a differential pattern is discovered, further steps to identify possible markers can be followed and possibly result in the development and validation of novel target methodologies. To this aim, authenticated voucher specimens, representative of the sample (plant or extract), are of utmost importance in untargeted methodologies. However, as medicinal plants are highly complex and their natural variations (due to geographical, seasonal, and environmental conditions, but also due to harvest period, processing, and storage, among others) can affect fingerprints, data exploration can be highly challenging. As hybrid HRMS detectors allow the acquisition of fragmentation data, they can assist in structure elucidation and identification of unknown metabolites. An overview of the workflow of untargeted metabolomics toward establishing novel biomarkers is thoroughly described in previous review papers (Dou et al., 2022; Lacalle-Bergeron et al., 2021; Zhong et al., 2022).

3.3.1 | Flow-injection mass spectrometry and ambient MS

Recently, different MS platforms have evolved as attractive alternatives to the current LC– or GC–MS untargeted approaches. Fingerprinting techniques such as flow-injection mass spectrometry (FIMS) and those using ambient ionization, including direct analysis in real-time mass spectrometry (DART-MS) and liquid microjunction surface sampling–HRMS, have been proposed as untargeted approaches for the authenticity assessment of PFS (Table 4). Both techniques have the advantage of requiring minimal or no sample preparation, thus enabling a high-throughput analysis. In FIMS, an autosampler is used to directly inject the sample into the mass spectrometer, without using a chromatographic column. It has the potential of identifying ions related to individual metabolites from the variable loadings obtained by applying chemometric analysis (Beckmann et al., 2008; Harnly et al., 2016, 2017; Nanita & Kaldon, 2016). In general, PCA, soft independent modeling of class analogy (SIMCA), and partial least squares-discriminant analysis (PLS-DA) are the applied multivariate analysis tools to construct suitable models to be used with FIMS (Harnly et al., 2017). Overall, the system determines if the fingerprinting patterns of unknown samples correspond to the reference ones (Beckmann et al., 2008; Harnly et al., 2016, 2017). FIMS provides fast analytical results as it does not require chromatographic separation and respective data processing such as the classical retention time alignment; however, the simultaneous introduction of numerous ions in the MS can lead to ion suppression/competition and typically reduces the sensitivity of the analyses (Liu et al., 2022). Moreover, the technique generally presents a poor reproducibility since the total of ion counts is highly dependent on the ionization efficiency. This limits its applicability as the fingerprints of unknown and reference samples must be obtained in the same assay under equal conditions (Harnly et al., 2016; Liu et al., 2022). Consequently, a large amount of reference samples is required because each time a new analysis is needed, the fingerprint of the reference samples must be acquired.

Different works report the applicability of FIMS for the authentication of plant materials in PFS. Sun and Chen (2011) proposed the use of FIMS coupled to PCA to survey skullcap (*Scutellaria lateriflora*)-containing PFS sold

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in the United States and detect adulterations with germander (*Teucrium canadense* and *Teucrium chamaedrys*), which are known to contain hepatotoxic diterpenes and are morphologically identical to skullcap. The method was able to successfully detect Chinese Skullcap (*Scutellaria baicalensis*) in one of the samples, while the other four were revealed to contain *T. canadense* jeopardizing the health of consumers. The authors confirmed the results by UHPLC–HRMS, proving the utility of the developed FIMS methodology (Sun & Chen, 2011). Harnly et al. (2017) applied FIMS to verify the presence of *Echinacea purpurea* aerial parts in 19 PFS claiming to contain this ingredient. The method was combined with PCA and *F*-test spectra, obtained from the *F*-value for each ion, to identify the discriminating ions found in both the botanical ingredients and the commercial PFS, while the correlation spectra allowed to verify the presence of the aerial part of the plant. The presence of *E. purpurea* was verified in five out of six single-ingredient PFS and in seven out of 13 PFS containing mixed plants. Spectral fingerprints acquired by FIMS coupled to SIMCA or fuzzy optimal associative memories (FOAM) have been also proposed to detect Asian ginseng (*P. ginseng*) as an adulterant of America ginseng (*P. quinquefolius*) (Harnly et al., 2013) and coupled to PLS-DA or fuzzy rule-building expert system to differentiate three *Panax* species (*Panax ginseng*, *Panax quinquefolius*, and *Panax notoginseng*) with 100% accuracy (Chen et al., 2011).

Similar to FIMS, DART-MS has shown the ability to quickly and easily analyze highly processed matrices such as foods, without requiring previous sample preparation, thus being suitable as a screening approach (De Angelis et al., 2021). DART analysis is seen as a promising and foreseeable technique in the near future for applications in species identification, food authenticity, herbal medicine, and botanical analysis, as deemed rapid quantification, high-throughput active compounds screening, and fast approach for illegal additives screening (Abraham & Kellogg, 2021; Shen et al., 2016). Moreover, as for other ambient MS techniques, the great advantage of DART-MS relies on its potential for in situ analysis since sample surfaces can be analyzed directly (Liu et al., 2022). The combination of DART-MS fingerprinting with multivariate analysis is showing great potential in the authenticity assessment of botanicals and PFS.

Lee et al. (2012) proposed the use of a novel DART–TOF-MS fingerprinting coupled with chemoinformatic tools to distinguish closely related Umbelliferae (Apiaceae) medicinal plants, including the very similar *Angelica gigas*, *A. dahurica*, and *Cnidium officinale* roots described in the Korean pharmacopoeia. The method allowed the rapid and effective differentiation of the species with no sample preparation (Lee et al., 2012). Although DART is usually coupled to TOF analyzers, it is also suitably combined with orbitrap mass analyzers as described by Li, Liu, et al. (2017) to assess the quality of Yuanhu Zhitong tablet (YZT), which is a traditional herbal Chinese medicine used for easing the pain owing to its content of Radix Angelicae and Rhizoma Corydalis. DART–Orbitrap MS combined with multivariate statistical analysis (PCA and PLS-DA) proved to be suitable for QC of YZT and was able to identify analytical markers, such as alkaloids and N-containing metabolites mainly originated from Rhizoma Corydalis, proving to be a fast and powerful tool to authenticate herbal products (Li, Liu, et al., 2017).

3.3.2 | Liquid chromatography

Currently, LC–MS methodologies are the most widely applied in bioanalytical analyses due to their broad covering range, providing identification and detection of a vast number of molecules (Ren et al., 2018; Theodoridis et al., 2012; Tian et al., 2022). As mentioned, hybrid HRMS is the most suited system for untargeted approaches as it provides a holistic approach to the detection of compounds, with the advantage of allowing for retrospective analysis of the data acquired in full scan mode, without the need for a new injection (Dou et al., 2022; Lacalle-Bergeron et al., 2021; Zhong et al., 2022). Thus, the obtained MS data can be used for advanced chemometrics to check for patterns and similarities/differences among reference and unknown samples, which can also be used to identify the compounds that comprise the fingerprint or identify potential chemical markers. Among the mass analyzers that have been coupled to LC separation for untargeted analysis, those comprise mainly Q-Orbitrap or Q-TOF-MS instruments (Table 4). Regarding the chromatographic systems, in the last decade, a growing number of works have applied UHPLC owing to its faster and more efficient separation of compounds than HPLC. According to some authors, the hybrid systems involving the Q-TOF-MS are the most appropriate for fingerprinting plant metabolites when combined with UHPLC due to its fast data acquisition, besides providing high sensitivity and mass accuracy (Theodoridis et al., 2012).

Avula et al. (2020) carried out an untargeted UPLC–Q-TOF-MS analysis to obtain the chemical fingerprint of crude extracts from different plant parts of *Vangueria agrestis* (Syn. *Fadogia agrestis*), a shrub indigenous to tropical Africa whose stems are traditionally used for treating fever, pain, and malaria. The PLS-DA score plot of the data acquired in negative mode showed the separation of the root, stem, leaf, and mixed parts. Moreover, the obtained loading plot identified the compounds responsible for that differentiation, evidencing the prevalence of

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triterpene saponins in the roots, flavonoids and monoterpene glycosides in the leaves, and pomolic acid glycoside derivatives in the stem samples. When analyzing seven PFS, the results suggested they contained stems as they clustered close to those samples, thus confirming the label of two products that claimed to include *V. agrestis* extract. In addition, 73 compounds were identified, from which 20 were confirmed with the corresponding standards, and the remaining were tentatively identified based on accurate MS and generated fragment ions (Avula et al., 2020). A similar approach was followed by Avula, Bae, Wang, et al. (2021) to verify the presence of *Bulbine natalensis* in nine PFS claiming to contain this species as a single plant ingredient. The chemical fingerprint of *B. natalensis*, *Bulbine frutescens*, and commercial samples obtained by LC–Q-TOF-MS were used for pattern recognition by PCA and PLS-DA, allowing to separate the two species in different clusters and to evidence that four samples did not contain any of these species. Moreover, the MS data obtained were used to identify 55 anthraquinone-type compounds, including 11 compounds confirmed with the corresponding standards, which can be useful not only for authentication purposes, but also to better understand the biological activity of this species.

Untargeted UPLC–Q-TOF-MS analysis coupled to PCA was also successfully used to differentiate three *Panax* sp. roots obtained from the American Herbal Pharmacopoeia and verify the botanical origin of two commercial PFS: one claimed to contain encapsulated North American ginseng root cultivated in Sandy City was confirmed as *Panax quinquefolius*, and the second product, a liquid vial claiming to contain red *Panax ginseng* cultivated in China, was also verified to contain the correct species (Yuk et al., 2016). Shin et al. (2021) proposed an untargeted approach by UPLC–Q-TOF-MS/MS to analyze three PFS and one sample of raw ingredient of tejocote root (*Crataegus mexicana*), a species of hawthorn sold as a weight-loss supplement. The PCA clustered the samples in two distinct groups. MS data identified cardiac glycosides thevetin B, neriifolin, and digitoxigenin in two samples, which were attributed to yellow oleander (*Thevetia peruviana*) by DNA barcoding, a plant known to be highly toxic, while the botanical origin was confirmed as *C. mexicana* for the two samples in the other cluster. Farag et al. (2013) applied PCA to data obtained from UPLC–Q-TOF-MS analysis of nine commercial St. John's Wort (*Hypericum perforatum*) PFS. Contrary to most untargeted approaches, the authors did not use any reference sample in this study; however, the PCA plot demonstrated that three PFS presented a slightly different profile due to fatty acids, which in one product could be attributed to other ingredients such as soybean. Moreover, the results did not evidence clusters attributable to differences in hypericins, possibly because their content can be standardized, thus exhibiting small variations among different brands.

The usefulness of untargeted metabolomics to analyze samples when with scarce information, such as commercial PFS, was also demonstrated by Wallace et al. (2018). Untargeted metabolomics using an LC–Q-Orbitrap system was carried out in a wide range of commercial goldenseal (*Hydrastis canadensis*) products, including 19 capsules, nine tinctures, eight powdered bulk materials, and two bagged infusions, in addition to four authentic samples of leaves and rhizomes. Despite the variability among products that could complicate pattern recognition, most of them clustered with *H. canadensis* references, with three samples falling outside the 95% confidence interval and being considered outliers. The PCA loadings plot revealed that the large cluster of the *H. canadensis* reference samples together with most PFS were separated from the outliers along principal component 1 (PC1), mainly due to two ions (m/z 384.1459 $[M+H]^+$ and m/z 340.1537 $[M+H]^+$), which were identified as hydrastine and canadine. Detailed analysis of the three outlier chromatograms confirmed the absence of these two alkaloids, supporting the hypothesis of sample adulteration. To further disclose the adulterants, the distinctive metabolites, as revealed by the PCA loading plot, were tentatively identified. MS data suggested the presence of coptisine, palmatine, and their ^{13}C isotopes, which were previously found in other berberine-producing species considered the most common adulterants of goldenseal. Therefore, reference materials of the root and rhizome of *Coptis chinensis*, the leaf and root of *Mahonia aquifolium*, and the root of *Berberis vulgaris* were additionally analyzed and incorporated into the metabolomic and statistical analyses. The results highlighted the similarity of one sample *with B. vulgaris*, another with *M. aquifolium*, and another with *C. chinensis*. The extracted ion chromatograms of the sample that clustered closely to *M. aquifolium* also identified jatrorrhizine, which is known to be present in this species, while all had coptisine and palmatine that are absent in goldenseal. Therefore, besides identifying three potentially adulterated samples without any prior knowledge of their composition, untargeted metabolomics also allowed us to successfully investigate the botanical origin of the adulterants.

An LC–Q-Orbitrap system was also exploited by Cruz et al. (2020), who demonstrated the importance of using representative reference samples in the untargeted analysis of *G. biloba* products. In this study, the National Institute of Standards and Technology (NIST) Standard Reference Materials (SRM) of *G. biloba* leaves and extracts were used for benchmark comparison of two sample sets composed of 16 plant materials and 16 dried leaf extracts. The samples of the first set included untreated and

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steam-treated ginkgo leaves from the same supplier and stem from a different source, while the dried leaf extracts were collected from different commercial manufacturers and included different water:solvent extractions. The samples were then adulterated at NIST with known levels of adulteration (3%, 7%, and 15%), randomly labeled and analyzed by LC–HRMS in the positive and negative modes combined with PCA as an unsupervised exploratory method. For the set of leaf samples, although the separation was not distinct in terms of percentage of adulteration, in the positive ion mode the variable with the highest loading that differentiated the adulterated samples was identified as sophoricoside, a compound present in *Sophora japonica*, a species described as a potential ginkgo adulterant. In the negative mode, the loadings that contributed most significantly to discriminating the adulterated samples were found to be sophoricoside and genistein. The authors concluded that the results were promising, but to improve the robustness of the PCA models, additional authentic samples would need to be included. With regard to the set of extracts, the results were not as promising because no differentiation was obtained either using the data obtained in positive, negative, or both combined modes. In this case, the type of extraction seemed to overshadow the adulteration level since different clusters were obtained for the aqueous, ethanol:water, acetone:water, and acetone:water with lecithin extracts, independently of the adulteration level. In the same way, the SRM extract showed to be very different from the remaining samples. These results might be attributed to differences in the provenance and preparation of the extracts, with varied composition being related to the different extracting solvents. This work demonstrates that when compared to raw materials/leaf samples, the classification of processed extracts can be more challenging since the manufacturing process may contribute to increasing the complexity of the analysis.

3.3.3 | Gas chromatography

Despite the limitations of GC–MS due to the poor capacity of analyzing polar, large-molecular-weight, and/or nonvolatile compounds, its high resolving power, high sensitivity, and the availability of spectral databases of great quality that facilitates the identification of metabolites are the main strengths (Kaklamanos et al., 2020; Theodoridis et al., 2011). GC–MS has been widely applied to obtain chemical fingerprints of volatiles in different samples. Nevertheless, its use as an untargeted approach in the analysis of PFS is not much reported in the literature. Untargeted metabolomics using this technique generally generates a large quantity of information comprising chromatographic and spectral datasets, thus data mining tools are often required. Wang et al. (2014) applied untargeted GC–MS to analyze 27 authenticated samples of three types of chamomiles, German (*M. recutita*), Roman (*C. nobile*), and Juhua (*Chrysanthemum morifolium* Ramat.), and constructed a sample class prediction model based on stepwise reduction of data dimensionality followed by PCA and PLS-DA. After cross-validation, the predictive model based on PLS-DA was employed to classify several commercial samples labeled as containing chamomile (11 essential oils and 35 solid products including flowers, powders, extracts, infusions, and PFS). Most of the samples displayed confidence measures above 0.7, indicating a high degree of certainty in the classification, with only seven samples presenting lower values. Among them, four had very few peaks, which could be related to the age and storage of the samples leading to the loss of volatile components. In general, the predicted classification was consistent with the labels, with all samples from the United States being identified as German chamomile, while those from China were identified as Juhua. In addition, the identification of marker compounds was attempted by data interpretation from the class prediction analysis, which showed to be consistent with the markers reported in the literature. Recently, Farag et al. (2022) used three analytical platforms, including solid-phase microextraction (SPME) coupled to GC–MS, to evaluate five authenticated *Cinnamomum* sp. materials (*Cinnamomum cassia*, *Cinnamomum verum*, *Cinnamomum iners* [Malaysia], *Cinnamomum tamala*, and *Cinnamomum verum* [Pakistan]) and four commercial products as cinnamon-containing PFS. The dataset comprising a total of 126 peaks obtained by SPME/GC–MS was subjected to unsupervised and supervised multivariate analysis, showing that two products were closer to *C. cassia* (Chinese cinnamon), while the other two were possibly derived from higher grade sources such as *C. verum* (true or Ceylon cinnamon). In terms of the origin of commercial products, UV/Vis showed low discrimination power, while GC–MS resulted in better models.

4 | CONCLUSION AND FUTURE PERSPECTIVES

Currently, consumers are increasingly concerned about healthy lifestyles and interested in products that contribute to health maintenance. Concomitantly, the variety and number of PFS easily available on the market have increased exponentially in the last decade. Due to the growing market demand and the high value associated with this type of product, they are attractive targets for economically motivated adulteration. In the last years, several

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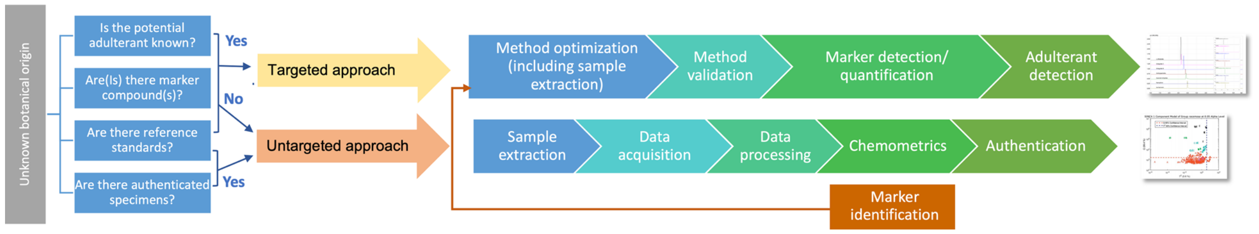

FIGURE 1 Workflow of targeted and untargeted analysis by liquid chromatography coupled to mass spectrometry for the botanical authentication of PFS.

reports from governmental agencies and a high number of published works focusing on this issue have clearly highlighted this problem. They have shown that two types of frauds are the most common in PFS, namely, the addition of pharmaceutical substances and botanical-origin adulteration. This last can be due to substituting plant species of higher value with others or arising from accidental plant swapping in the case of morphologically similar species. In any case, consumer health can be seriously compromised. Therefore, much progress has been made in recent years to detect such adulterations, benefiting from analytical developments that resulted in increasingly robust, sensitive, fast, and advanced techniques. Various types of MS analyzers, commonly hyphenated with chromatographic separation of compounds, have been demonstrating their effectiveness in detecting PFS adulteration, either by targeted or untargeted approaches. So far, most works have relied mainly on the use of targeted approaches, mainly by qualitatively and quantitatively profiling a group of characteristic compounds for a particular species. One of the most studied plants in terms of profiling methodologies is *G. biloba* because its extracts are generally standardized in terms of flavonoids and terpene lactone contents. Interestingly, over the years, several advances and improvements have been proposed in these methods to respond to the need of detecting new frauds in the sector: from just determining the three principal aglycones after hydrolysis to the proposal of ratios and, later, to the individual determination of several compounds from ginkgo's two major groups of bioactives in a single run.

LC–MS is currently used to carry out either targeted or untargeted analysis aiming at the botanical authentication of PFS. Overall, the most suitable approach should be selected on a case-by-case basis, relying on the available information, particularly on the known potential adulterant species and respective markers, but also on other aspects such as the availability of reference standards and authenticated voucher specimens (Figure 1). Targeted methodologies will certainly remain one of the most straightforward approaches, particularly when based on the identification of specific adulterant marker compounds, whose presence unequivocally identifies the adulteration. With further developments in analytical technology, it is expected that hyphenated targeted MS analysis will further improve in terms of throughput, sensitivity, and selectivity, due to additional advances in data acquisition speed and sensitivity, new chromatographic stationary phases, and so forth. However, so far, only a few markers of botanical adulterants are known. With the rising availability of advanced hyphenated HRMS equipment and its increasing application to the analysis of raw botanicals, extracts, and PFS, one can anticipate a higher number of marker compounds to be discovered in the future. HRMS can provide large amounts of data, resulting in detailed chemical fingerprints, but it also enables the structural identification by exact mass and MS/MS fragmentation. Moreover, compounds with significant differences among samples can be revealed when combined with chemometrics. This can ultimately lead to the identification of new markers for adulterants, which after being validated for their specificity and universality can result in the development and validation of new targeted methods (Figure 1). Untargeted fingerprinting has also the advantage of not requiring any prior knowledge about the sample and possible adulterants and being able to pinpoint outliers in large sample sets for which scarce information is available (Figure 1). However, one cannot forget that the complexity of natural products and the natural variation of the chemical constituents in plant species may impart limitations to fingerprinting methods coupled with multivariate statistics, particularly for borderline samples. Nevertheless, untargeted metabolomics based on HRMS is undoubtedly a powerful tool for the analysis of complex matrices such as plant extracts and PFS, thus with high potential of being increasingly used in this field. Finally, considering that frauds can happen along the whole value chain, from the collection of the raw materials to the commercialization of the final product, the development/availability of portable and fast techniques that can be used at the point of need (e.g., in the field, warehouses, at customs, etc.) will be increasingly requested. To address this need, the miniaturization of mass spectrometers using ambient ionization to be applied in authentication studies may be a potential alternative.

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AUTHOR CONTRIBUTIONS

Liliana Grazina: Investigation; writing—original draft. **Isabel Mafra**: Conceptualization; writing—review and editing; formal analysis; supervision; visualization; resources. **Linda Monaci**: Writing—review and editing; formal analysis; supervision. **Joana S. Amaral**: Conceptualization; supervision; formal analysis; writing—review and editing; writing—original draft; funding acquisition; resources; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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