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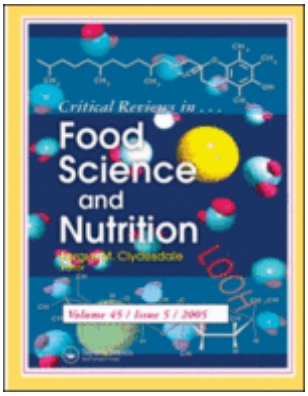

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Herbal products comprise a wide spectrum of locally, nationally or internationally commercialized commodities. As these products have an increasingly important position in healthcare systems worldwide, a detailed product quality assessment is of crucial importance. A wide range of methods were used, from simpler, quicker and cost-effective TLC, HPTLC or HPLC to hyphenated methods with MS or NMR, where more precise quantification or specific structural information is required. Additionally, most of the methods have been coupled with chemometric tools, such as PCA, or PDA, for the multivariate analysis of the high amount of data generated by chromatograms, electropherograms or spectra. The chemical methods have revealed the widespread presence of low or variable quality herbal products in the marketplace. The majority of analytical investigations present major, qualitative and quantitative, inter-product variations of their chemical composition, ranging from missing ingredients, to strikingly and unnaturally high concentrations of some compounds. Moreover, the inter-batch quality variations were frequently reported, as well as the presence of some undesirable substances. The chemical analysis of herbal products is a vital component to raise the overall awareness of quality in the herbal market and help to generate a more quality driven approach.

Keywords: chemical composition, food supplement, herbal medicine, phytochemicals, quality control, food safety.

Introduction

Herbal products (HPs) comprise a wide spectrum of locally, nationally or internationally commercialized commodities, mainly categorized as medicines or food and dietary supplements (Thakkar *et al.*, 2020). Their marketing names often depend on their final declared use, regulatory requirements and prevailing national legal frameworks and are presented under many marketing terms (Ichim, 2019). Yet, all HPs have to comply with many statutory requirements relating to their manufacture, constitution, testing, storage and distribution (Zöllner and Schwarz, 2013).

In the global marketplace, HPs are presented for commercialization under an even wider array of forms, from the more traditional loose-dried herbs, loose and bagged tea, extracts, decoctions, infusions, poultices, essential oils, tinctures, glycerites, powders, pills, tablets, capsules, drops, softgels and syrups (Zöllner and Schwarz, 2013; Grosu and Ichim, 2020), to some specific products such as toothpastes, cigarettes, soaps, cosmetics, beverages (including energy drinks or beer), coffee, baby food, candies, and chewing gum (Morgan and Cupp, 2000).

A widespread misconception exists amongst consumers that "natural" always means "safe" (World Health Organization, 2004). Even though the public is often misled to believe that all-natural treatments are inherently safe, herbal remedies do carry similar, quality related, risks to other products, including allopathic medicines (Posadzki *et al.*, 2013). Due to quality issues, such as the use of poor-quality herbal starting materials, incorrect or misidentified herbs, incorrect processing, manufacturing and storage methods, adulteration or contamination of starting materials or products, there is an ongoing problem with some herbal products' unexpected toxicity (Başaran *et al.*, 2022), as well as potential lack of desired effects.

This rooted common belief that herbal products are always safe to use, sometimes leads to serious, or in some cases even lethal, adverse reactions (ADRs) and herb-drug interactions (Gouws and Hamman, 2020). Several widely used herbal products are known to interact with specific drugs, including St. John's Wort (*H*ypericum *perforatum* L.), ginkgo (*Ginkgo biloba* L.), ginger (*Zingiber officinale* Roscoe), ginseng (*Panax ginseng* C.A.Mey), and green tea (*Camellia sinensis* (L.) Kunze) (Awortwe *et al.*, 2018). A systematic assessment of potential ADRs and interactions is lacking for the majority of the herbs that are not commercialized as medicines. Apart from idiosyncratic reactions, the majority of adverse events related to the use of herbal products are due either to poor product quality or to improper use. Inadequate regulatory measures, poor quality control systems and largely uncontrolled distribution channels (including mail order and Internet sales) may have been contributing to the occurrence of such events (Shetti *et al.*, 2011).

The safety and efficacy of HPs largely depend on their quality (World Health Organization, 2018). The safe use of the HPs can be significantly hindered, or even totally compromised, by the presence of unlabeled botanical or chemical contaminants and adulterants or by the overall low quality of these products. The rapidly accumulating body of scientific evidence is demonstrating what was long suspected: the adulteration of commercial herbal products is substantial and represents a globally widespread problem (Ichim, 2019).

All of the authentication methods, when employed for species identification in commercial herbal products, have revealed their own strengths and limitations. Microscopy is a rapid and cost-efficient method, which can cope with mixtures and impurities but has limited applicability for the botanical authentication of highly processed herbal samples (Ichim *et al.*, 2020).

DNA barcoding was already accepted as an official pharmacopeial plant identification method (Pharmacopoeia Committee of P. R. China, 2015; British Pharmacopoeia Commission, 2018), and the DNA metabarcoding, the combination of high-throughput sequencing (HTS) and DNA barcoding, enables untargeted, simultaneous multi-taxa identification by using the DNA of different origins extracted from complex mixtures and matrices (Raclariu *et al.*, 2018). Such approaches are limited by the high sensitivity for any amplifiable DNA isolated from the product, the quality of the isolated DNA (Harnly *et al.*, 2015) and, most importantly, by the inability to distinguish which plant part is in the product examined, based on DNA material. The root of *Rheum palmatum* L. is used as medicine, while the stalks are used as food. Different parts of the plant contain different amounts or types of compounds, thereby often having different effects.

On the other hand, chemical methods, the most important and widely used traditional plant identification and quantification techniques, recommended by national and international pharmacopeias, are versatile and can be the only possibility for assessing the botanical authenticity of samples which have lost their diagnostic microscopic characteristics or were processed so that DNA cannot be adequately recovered (Harnly *et al.*, 2015; Ichim and Booker, 2021), as well as remaining able to distinguish between materials coming from the same species but different plant parts, based on the chemical fingerprints and relative concentrations of metabolites contained within those parts.

Various analytical methods have identified the total absence of labeled botanical ingredients, substitution with closely related or unrelated species, the use of biological filler material, and the hidden presence of regulated, forbidden or allergenic species in commercial herbal products (Ichim, 2019; Ichim *et al.*, 2020; Ichim and Booker, 2021). Additionally, HPs were reported to

contain many other harmful contaminants and residues, such as dust, insects, rodents, parasites, microbes, fungi, molds, mycotoxins, pesticides, poly aromatic hydrocarbons (PAHs), heavy metals, radioactivity, processing impurities, solvent residues, and illegal or prescription drugs (Jordan *et al.*, 2010; Posadzki *et al.*, 2013).

As herbal products have an important position in healthcare systems worldwide, their current assessment and quality control are a major bottleneck (Tistaert *et al.*, 2011). Their safety has become a concern to both national health authorities, medicine regulators and the general public (World Health Organization, 2004; MHRA, 2014).

As a consequence, robust safety assessments must be a priority for manufacturers and suppliers of botanicals and botanical preparations intended for use as ingredients in phytopharmaceuticals and food supplements (Zöllner and Schwarz, 2013). Irrespective of their botanical composition and dosage form, commercial HPs are complex mixtures with a naturally variable number and amount of chemical compounds within an uncharacterized matrix (Meier and Spriano, 2010; Balekundri and Mannur, 2020); they are multicomponent systems and this represents a complication in the evaluation of their chemical quality, when compared to products with a known single active ingredient. The effectiveness and safety of the final herbal preparation is based on the quality and the profile of the components of the formulation, first and foremost the quality (and identity) of raw starting materials, which are known to naturally vary based on. different physical, chemical, and geographical aspects (World Health Organization, 2018; Balekundri and Mannur, 2020).

As a result, requirements and methods for the quality control of finished herbal products, particularly for mixture herbal products, are far more complex than those for pharmaceuticals (World Health Organization, 2018). In this respect, our review identifies and details those

analytical methods which were successfully used for detecting the low or variable quality of many herbal products from the global marketplace.

Literature databases: search strategy and selection process

Search strategy

Four databases were systematically searched for peer reviewed records following the PRISMA guidelines (Moher *et al.*, 2009) using combinations of relevant keywords, Boolean operators and wildcards: [("herbal product" OR "herbal medicine" OR "traditional medicine" OR "food supplement" OR "dietary supplement" OR "herbal supplement" OR nutraceutical) AND (authentic* OR contaminat* OR substitut*)] for Web of Science, PubMed, Scopus, and [("herbal product" OR "herbal medicine" OR "food supplement" OR "dietary supplement" OR "herbal supplement" OR nutraceutical) AND (authentication OR contamination OR substitution)] for ScienceDirect. The option "search alert" was activated for all four databases, to receive weekly updates after the literature search was performed. Furthermore, cross-referencing was used to identify additional peer-reviewed publications.

Selection process and criteria

Identification: 10,497 records were identified through database searching (WoS = 1,317, PubMed = 3,253, Scopus = 5,446, and ScienceDirect = 481), and 202 additional records through cross-referencing from other sources, including the records received weekly through email from the four databases.

Screening: 2,332 records were retrieved and their abstracts screened after the duplications had been removed. After screening, 1,746 records were excluded for not reporting data relevant for the chemical authentication of herbal products.

Eligibility: *586* full-text articles were assessed and screened based on the following six eligibility criteria:

1. The reported products had to be "herbal products" *sensu lato*. The full wide range of commercial names was searched for and accepted for being included in our analysis.

2. The analyzed products had to be "commercial". Keywords such as "purchased", "bought", were accepted, no matter if the samples came from a local or traditional market, herbalist shop, health food store, supermarket, pharmacy, etc., purchased under prescription, freely over-the-counter or via internet. Our analysis excluded studies where the analyzed samples were obtained "cost-free", a "gift" or "donated" by a person, institution or company.

3. The products had to be clearly allocated to a "country" or "continent". We have reported the country/continent from which the products were purchased or received after they were ordered on the internet.

4. The products had to be analyzed with a "chemical method or technique", using any "natural compound" as authenticity or quality marker. When other methods (e.g., microscopic examination, DNA-based analysis) were used to test the authenticity and quality of the products, we took into consideration the chemical-based results only, as they were distinctively reported by authors.

5. The reported herbal products had to be free of any botanical contamination or adulteration as it was reported in the reviewed publication. This ensures that the reported quality issues are not due to unlabeled botanical ingredients.

6. The conclusions about the quality issues had to be drawn by the authors of the analyzed studies. Their exact wording was used to describe the quality of the products (in Table 1).

The set of retrieved full-text articles was further reduced by *446* that did not meet all six eligibility criteria.

Included: *46* records.

Our systematic literature search has identified 46 peer-reviewed publications, each of them reporting the results of analyzing 18 herbal products in average, the number largely varying from 2 (Govindan and Govindan, 2000) up to 59 commercial samples (Pawar *et al.*, 2020).

Quality assessment using chemical methods of commercial herbal products: an overview

A total of 727 herbal products were chemically analyzed to assess their quality in comparison with the label-declared composition (Table 1). Only the products for which there was no contamination or adulteration with unlabeled botanical ingredients reported were included in the analysis so that the identified quality parameters should not have been, either positively or negatively, influenced by off-label ingredients.

The highest number of commercial herbal products was purchased from North America (n = 334), followed closely by Europe (n = 216), Asia (n = 136), and more distantly by South America (n = 22) and Africa (n = 19) (Table 2). Located on the five continents, the tested commercial samples were purchased from 29 countries (Table 3), which further contributed to a relevant geographical distribution of the reported results. For almost half of the total number of countries (n = 14) at least 10 (n ≥10) commercial herbal products were successfully tested.

Herbal products: a highly heterogeneous category of commercial commodities

Herbal products are commercialized in the global marketplace under many and diverse names deriving from the prevailing regulatory framework under which they are marketed (Simmler *et al.*, 2018); these include herbal drugs, botanical drugs, botanicals, phytomedicines, traditional medicines (TMs), herbal medicines (HMs), traditional Chinese medicines (TCMs), traditional herbal medicinal products (THMPs), natural health products (NHPs), nutraceuticals (NCs), dietary supplements (DSs), or plant food supplements (PFSs) (Ichim, 2019). Nevertheless, in

spite of the marketing descriptions, the herbal products fall under two main categories: medicines and foods, being purchased for their claimed or only expected health benefits (Thakkar *et al.*, 2020). The significant differences between the regulatory approaches across jurisdictions (Low *et al.*, 2017), are contributing to their poor regulation on the international market. The World Health Organization (WHO) has estimated that these differences contribute to the presence of counterfeit, poor quality, or adulterated herbal products in international markets (Wheatley and Spink, 2013; Osathanunkul *et al.*, 2018).

The details provided by the authors of the reviewed reports (Table 1) fully confirm the wide range of commercially available products. In the most relevant countries from Asia (e.g., Taiwan) (Lin *et al.*, 2015) and South America (e.g., Brazil) (Beltrame *et al.*, 2009) the large majority of the herbal products are traditional medicines (Yao *et al.*, 2016).

The commercial herbal products tested are presented mostly as loose raw plant materials (e.g., chopped or powdered leaves, flowers, roots and rhizomes) (Alvarenga *et al.*, 2009; Sharma *et al.*, 2015) and either as single- (Dias *et al.*, 2013) or multi-botanical ingredient products, as the ones used in traditional Chinese medicine. On the other side, the majority of the products from North America and Europe are commercialized as single-ingredient herbal food supplements (Jiao *et al.*, 2010; Boudesocque-Delaye *et al.*, 2018; Pawar *et al.*, 2020) and commercialized as pre-packaged tea bags (Raal *et al.*, 2012), instant teas (Bilia *et al.*, 2002), liquid extract, tincture (Gao *et al.*, 2008), tablets, capsules (López-Gutiérrez *et al.*, 2016), pressed juice (Osowski *et al.*, 2000), syrup (Sánchez-Patán *et al.*, 2012), drink powder (Pawar *et al.*, 2020), etc.

All these different commercial products were purchased from herbal markets, drug stores, producer's plant cultivation, herbal practitioners, pharmacies, herbal shops, manufacturers, etc. This wide range and long string of individuals and entities which sold the analyzed products

confirm the complexity of herbal products' value chains, irrespective if they are sourced by a short, local one or by a long, national or even international chain of production and trade (Booker *et al.*, 2012). The complexity of both forms under which the herbal products are marketed around the globe, i.e., food supplements and medicines, and of their value chains increases the difficulties of their quality evaluation for ensuring their labeled and expected safety and efficacy.

Reference plant materials and standards used for chemical assessment

For the evaluation of the chemical composition and overall quality of herbal products the use of reference materials, chemical standards or pharmacopeial information is of paramount importance. Reference standards are an important tool not only to ensure analytical quality and method transfer but also to guarantee the safety of herbal products, including the raw material, extracts, pharmaceutical formulations and food or dietary supplements (Zöllner and Schwarz, 2013). Reference materials refer to materials other than substances appropriate for intended uses in standardization or quality control of herbs and herbal materials, and include herbarium samples, authenticated specimens of herbal materials, herbal reference preparations (such as extracts and their fractions) and authentic spectra or fingerprints (World Health Organization, 2017).

In some of the reports reviewed, the authors have collected and authenticated plant material belonging to many different plant species, such as *Hypericum* sp. (Scotti *et al.*, 2019), *Garcinia* sp. (Seethapathy *et al.*, 2018a), *Bacharis trimera* (Beltrame *et al.*, 2009), *Mikania glomerata* (Alvarenga *et al.*, 2009), and *Ephedra sinica* Stapf (Gurley, 1998). Even more studies have relied on collected or purchased plant parts, instead of the entire plant, mostly being used the relevant plant part for the species of the commercial product under evaluation: flowers of *H. perforatum* (Farag and Wessjohann, 2012), fruits of *Foeniculum vulgare* Mill. (Bilia *et al.*, 2002), bark of

Pausinystalia johimbe (K.Schum.) Pierre ex Beille (Abourashed and Khan, 2001), roots and herbs of *Hydrastis canadensis* L. (Govindan and Govindan, 2000; Wang *et al.*, 2001), leaves, seeds and capsules of *Tanacetum parthenium* (L.) Sch.Bip. (Heptinstall *et al.*, 1992), leaves, twigs and bark of *Acacia rigidula* Benth. (Pawar *et al.*, 2014). As reference materials for the chemical analysis of commercial traditional Chinese medicines, authenticated samples and batches of crude and dried herbal drugs were used (Xu *et al.*, 2010; Avula *et al.*, 2014; Kim *et al.*, 2015) as well as in-house made standard preparations from commercial crude drug reference materials (Yao *et al.*, 2016). A comparable number of studies have used commercially authenticated or in-house prepared extracts and fractions from authenticated herbal materials collected or purchased, such as chamomile oil (Khattab *et al.*, 2010), and cranberry juice (Boudesocque-Delaye *et al.*, 2018). More studies have taken advantage of pharmacopeial and other commercially available standardized reference extracts from various species, such as St. John's wort dry extract, *G. biloba* extracts (Kressmann *et al.*, 2002; Deng and Zito, 2003), dried Silybum marianum (L.) Gaertn. Extract (Fenclova *et al.*, 2019), and *P. johimbe* extract (Lucas *et al.*, 2015).

Due to the previously observed limited amount and relatively high price of many authentic standard chemical markers (Indrayanto, 2018), the successful use of laboratory-obtained reference chemical standards was reported for the chemical assessment of ginkgo products (Ömür Demirezer *et al.*, 2014). Yet, the vast majority of the chemical evaluation studies have relied on primary and secondary commercial chemical reference standards, available for a large spectrum of medicinal plant species (Zöllner and Schwarz, 2013). A few investigators have instead relied entirely on the information provided by the corresponding national pharmacopeia, as the authoritative source of information for comparison of the obtained TLC fingerprints

(Beltrame *et al.*, 2009; Dias *et al.*, 2013). The availability of reference standards that are suitable for characterization of herbal preparations continues to be an ongoing global challenge (Zöllner and Schwarz, 2013), and many more such new pharmacopeial and non-pharmacopeial standard should become commercially available to all stakeholders interested in the quality control of the marketed herbal medicines and food supplements.

Chemical methods used for the quality assessment of commercial herbal products

Analytical methods used for quality control of herbal materials, herbal preparations and finished herbal products are generally based on wet chemistry methods, chromatographic procedures, spectroscopic and spectrometric methods and their combinations (World Health Organization, 2017). Several techniques have been established for the identification and quantification of marker compounds in herbal formulations but due to the complex nature of herbal formulations, chromatographic methods are commonly used to obtain what is considered a better representation of the chemical contents of a herbal product - a fingerprint: a profile of the different constituents within the herbal product (Kustrin and Hettiarachchi, 2014). Therefore, for the assessment and quality control of herbal products, chromatographic fingerprinting is the generally accepted, most widely used technique, long-time adopted and recommended by all national and international pharmacopeias (Tistaert *et al.*, 2011) and represent the techniques recommended by some food and medicine regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Fingerprinting methods include thin layer chromatography/high performance thin layer chromatography (TLC/HPTLC), high performance liquid chromatography (HPLC) and gas chromatography (GC), capillary zone electrophoresis (CZE) and micellar electrokinetic chromatography (MEKC). These techniques can be successfully complemented by spectroscopic techniques, including nuclear magnetic

resonance or mass spectrometry and representative results, comparable to those obtained by chromatography were also obtained using IR or UV–VIS spectroscopy (Sima *et al.*, 2018).

In the reviewed literature, commercial herbal products had their chemical composition analyzed with a wide variety of methods, many of them being the pharmacopeial-recommended ones for the labeled species. The quality control strategies applied to herbal products starts with quick, and thus cost-effective techniques (i.e., TLC, HPTLC or HPLC) used for primary qualitative analysis or alternatively using hyphenated methods (i.e., HPLC-UV, HPLC-DAD, HPLC-MS, GC-MC, or LC-NMR) to enable also the quantification of the lead or marker compounds (Raclariu *et al.*, 2018).

Single chemical methods

Thin-layer chromatography (TLC) is widely used for qualitative analysis to determine the number of components in a mixture or to determine the identity and approximate quantity of substances ((Hess, 2007) and is part of most modern herbal drug monographs (Meier and Spriano, 2010). TLC was successfully adopted for the chemical evaluation of all the traditional medicines purchases from Brazil (Alvarenga *et al.*, 2009; Beltrame *et al.*, 2009; Dias *et al.*, 2013) and a few goldenseal (*Hydrastis canadensis*) products from USA (Govindan and Govindan, 2000).

High-performance TLC (HPTLC) is a sophisticated instrumental technique, based on the full capabilities of TLC with increased reproducibility of results. Advantages such as automation, scanning, full optimization, selective detection principle, minimum sample preparation, and hyphenation, enable it to be a powerful analytical tool for chromatographic information of complex mixtures of natural products (Attimarad *et al.*, 2011). Peak profiles and their intensities, obtained from the HPTLC fingerprint images, can give both qualitative and quantitative results

in comparison with reference standards. Marker compound identification, percentage of purity, and minimum content information can also be obtained by this technique (Balekundri and Mannur, 2020). HPTLC analysis has successfully unveiled specific chemical differences among St. John's Wort (*H. perforatum*) products purchased from the UK (Scotti *et al.*, 2019). Chiefly a quantitative method but also used for "fingerprinting", high performance liquid chromatography (HPLC) was widely used in the reviewed studies for the chemical evaluation of the overall quality of the commercial herbal products. HPLC alone was able to reveal the quality variations in commercial multi-ingredient "Ojeok-san" granules from South Korea (Kim *et al.*, 2015), and extracts of *Scutellaria baicalensis* Georgi from Taiwan and China (Ye *et al.*, 2004). The same method was successfully applied to many different forms of food supplements sold in Western countries, containing a wide range of plant species as main botanic ingredients: *Echinacea* sp. (Osowski *et al.*, 2000), *H. perforatum* (Wurglics *et al.*, 2001), *T. parthenium*, *Scutellaria* sp. (Bailey et al., 2002), *G. biloba (*Kressmann et al., 2002), *Ginseng* sp. (Harkey et al., 2001), *Ephedra* sp. (Gurley, 1998; Gurley *et al.*, 2000), *H. canadensis* (Govindan and Govindan, 2000; Abourashed and Khan, 2001; Wang *et al.*, 2001). Moreover, HPLC - photodiode array (PDA) was used to quantitate five flavonol components from Ginkgo biloba products and the average marker content varied greatly (Dubber and Kanfer, 2004). Additionally, the reverse-phase HPLC (RP-HPLC), the most commonly used mode of HPLC when analyzing and attempting to separate and identify compounds from a complex mixture, was able to detect inconsistencies or even remarkable quality variations in traditional "guaco" products sold in Brazil (Alvarenga *et al.*, 2009) and ginkgo products from UK (Ding *et al.*, 2006), thus confirming the versatility of this chromatographic method.

Micellar electrokinetic chromatography (MEKC), a separation mode of capillary electrophoresis (CE) that has enabled also the separation of electrically neutral analytes, is a useful technique particularly for the separation of small molecules, both neutral and charged, and allows high-efficiency separation in a short time with minimum amounts of sample and reagents (Terabe, 2009). Several gingko samples (*G. biloba*) had their declared chemical composition assessed using reverse flow MEKC (RF-MEKC) (Dubber and Kanfer, 2006).

Nuclear magnetic resonance (NMR) was described as an effective tool for the quality control of medicinal plants or herbal medicinal products due to the relative ease of sample preparation, nondestructive analysis, potential to identify a broad range of compounds, enhanced capacity for definitive chemical compound identification, and provision of structural information for unknown entities(Booker *et al.*, 2014). NMR analysis of *Garcinia* food supplements revealed a large variation in the content of (−)-hydroxycitric acid content per capsule or tablet (Seethapathy *et al.*, 2018a), while it also detected significant differences among *A. vera* products for the contents of lactic acid and acetic acid (Jiao *et al.*, 2010).

The profiling and quantitative determination of compounds which can be vaporized without decomposition by gas chromatography (GC) is very important in the analysis of herbal products (Muyumba *et al.*, 2021). As an already established method, when the standard GC was used for the quality evaluation of saw palmetto products (*Serenoa repens* (W.Bartram) Small), based on the quantification of several fatty acids, it showed they varied significatively (Booker *et al.*, 2014).

Hyphenated chemical methods

Multiple chromatography hyphenated techniques have been used to acquire higher capacity and resolution for the analysis of medicinal plants, such as ultraviolet (UV) detection or photodiode

array detection (DAD), nuclear magnetic resonance (NMR) spectrometry, and mass spectrometry (MS) (Zhu *et al.*, 2018). Several types of tandem MS systems have been applied according to the optimal application ranges for different researches, including triple quadrupole (QqQ), ion trap (IT), and hybrid MS systems, such as the Q-TOF, Q-Orbitrap, LITOrbitrap, Q-ICR, LIT-ICR, etc. (Li *et al.*, 2021).

Liquid chromatography coupled to mass spectrometry (LC/MS), which combines the fast separation and accurate identification ability (Yao *et al.*, 2016), has been most used in both qualitative and quantitative analysis of herbal products (Sun *et al.*, 2017).

The analysis of ginkgolides by LC-MS in ginkgo food supplements showed that some products did not possess similar content as herbal medicinal products, and the quantity of the marker compounds per tablet/capsule was found to be lower than what declared on the labels (Ömür Demirezer *et al.*, 2014). The LC-MS/MS method, established to quantify natural and synthetic amines in bitter orange dietary supplements, has concluded that very few met claims for their label concentration declarations (Pawar *et al.*, 2020) while the analysis of several commercial ginseng preparations, from the genera *Panax* or *Eleutherococcus*, showed concentrations of ginsenosides that varied by 15- and 36-fold in capsules and liquids, respectively, and concentrations of eleutherosides that varied by 43- and 200-fold in capsules and liquids (Harkey *et al.*, 2001). The same method revealed significant differences in the amine profiles of dietary supplements containing *Acacia rigidula* extract when the quantitative determination of several phenethylamine, tyramine and tryptamine derivatives was carried out (Pawar *et al.*, 2014).

The development of various mass analyzers, such as quadrupole (Q), ion trap (IT), and time-of-flight (TOF), made MS applicable to global qualitative and quantitative analysis of herbal components in complex herbal matrices (Zhou *et al.*, 2009). The LC/QTOF-MS and LC/QQQ-

MS has been used to characterize and quantify yohimbine and its analogs in *Pausinystalia johimbe* products; extracts that contain yohimbine without its associated stereoisomers and analogs were detected, suggesting adulteration with yohimbine HCl (Lucas *et al.*, 2015).

The UPLC/QTOF-Fast DDA approach was used for the global profiling and characterization of multi-component products using multiple reference standards of several batches of traditional Shuxiong tablets and 250 compounds were identified or tentatively characterized, revealing low content of some markers possibly due to the employment of different preparation processes or of poor-quality drug materials (Yao *et al.*, 2016).

The ultra-high performance liquid chromatography (UHPLC), a version of HPLC which is using environment-friendly solvents, is less-time consuming, offers greater chromatographic resolution and higher sensitivity (Cielecka-Piontek *et al.*, 2013). The analysis of several nutraceutical products obtained from ginkgo using UHPLC-Orbitrap-MS and a database containing 65 compounds indicated a great variation of the amount of terpenoids among samples, and the presence of some undesirable substances such as ginkgolic acid (López-Gutiérrez *et al.*, 2016). High-throughput UHPLC-HRMS analyses of silymarin content in milk thistle-based dietary supplements were performed and large differences were observed among individual products, often in contrast with the information provided by the manufacturers, as well as substantial inter-batch differences. With the characteristics of wide suitability, high resolution, selectivity, sensitivity, and full automation, LC hyphenated techniques are indeed among the most useful and popular methods (Xu *et al.*, 2010).

Gas chromatography coupled with mass spectroscopy (GC–MS) is mainly used for the analysis of volatile constituents in medicinal plants and herbal products but various non-volatile compounds can also be analyzed after derivatization, such as amino acids, fatty acids, organic

acids, glucosamine, sugars, pyrimidine, and purine (Zhu *et al.*, 2018). The GC-MS analysis of the volatile constituents from some fennel teas revealed high levels of fenchone, suggesting the presence of bitter fennel or the presence of other parts of *Foeniculum vulgare* or other plants, suggesting the low quality of the products (Bilia *et al.*, 2002). The essential oils extracted from several commercial chamomile tea products were analyzed by GC-MS and their quality proved to be very variable (Raal *et al.*, 2012). The same method successfully revealed large variations of *Ephedra* alkaloid content within and between different product lines of dietary supplements (Baker *et al.*, 2003) and confirmed previous reports of inconsistent content of commercial *Ginkgo biloba* L. products when it was used for simultaneous identification and quantification of several marker compounds in ginkgo capsule phytopharmaceuticals (Deng and Zito, 2003).

Chemometrics

Chemometrics provide scientists with useful tools for understanding the huge amounts of data generated by the analytical advances and prove to be valuable for quality control, classification and modelling of, and discrimination between herbal fingerprints (Tistaert *et al.*, 2011). The holistic evaluation of the electropherograms, chromatograms or spectra can be achieved by using appropriate chemometric tools, multivariate exploratory techniques such as principal component analysis (PCA), cluster analysis and a combination of PCA and linear discriminant analysis (PCA-LDA) (Sima *et al.*, 2018). Comprehensive methods and hyphenated techniques associated with chemometrics used for extracting useful information and supplying various methods of data processing are now more and more widely used in medicinal plant research and quality evaluation of herbal products (Bansal *et al.*, 2014).

HPLC-ultraviolet (HPLC-UV) quantitative determination of peimine and peiminine in Fritillariae Thunbergii Bulbus products, followed by HCA, has allowed identification of the similarities and differences between the samples (Lin *et al.*, 2015).

HPLC–PDA determination and quantification of 19 compounds, followed by PCA and HCA analysis, was a useful strategy for quality evaluation of Ojeok-san traditional multi-herbal products as one or more marker substances were not present (Kim *et al.*, 2015). Principal components analysis (PCA), Hierarchical clustering analysis (HCA) and similarity analysis (SA) of main bioactive compounds identified and quantitated by HPLC-DAD in samples of Fructus Aurantii Immaturus (*Citrus aurantium* L.) has revealed evident concentration disparity of naringin and hesperidin in the herbal materials (Xu *et al.*, 2010).

UPLC-qTOF-MS was used to identify and quantify 21 specific metabolites from St. John's Wort products and PCA analysis was able to discriminate the variable quality of various preparations according to their global composition, including between batches from the same supplier (Farag and Wessjohann, 2012).

The UHPLC-MS/MS method was used for the quantitative determination of 20 bioactive compounds in Traditional Chinese medicine complex Wu Ji Bai Feng Pill products. When PCA and HCA were applied to evaluate intrinsic quality and to identify chemical markers relevant for quality evaluation, it was observed that the contents of the analytes differed significantly among different products (Duan *et al.*, 2019). Different types of red yeast rice (RYR) were analyzed using UHPLC–DAD–QToF-MS for their content in monacolins, pigments and citrinin, and PCA was able to discriminate between RYR dietary supplements due to ratios of monacolins that differed significantly from authentic samples (Avula *et al.*, 2014).

UPLC-DAD-ESI-TQ- MS, followed by PCA, revealed that cranberry products found in the market widely differed in their phenolic content and distribution, including products completely devoid of flavan-3-ols to highly purified ones (Sánchez-Patán *et al.*, 2012).

A PCA model of the ^{1}H NMR spectroscopy results was used to investigate saw palmetto products and it was able to provide some evidence that certain samples were adulterated with compounds not detected previously by GC analysis (mainly other plant oils) (Booker *et al.*, 2014). Additionally, the ^{1}H-NMR/PCA analysis of St. John's Wort products showed considerable differences in the products composition (e.g., flavonoids), inter-product and inter-batch variation (Rasmussen *et al.*, 2006) as it also detected did for feverfew products (*Tanacetum parthenium*) (Bailey *et al.*, 2002).

Digitally enhanced TLC (DE-TLC) easily and cheaply improved standard TLC by the application of digital color photography and image analysis (Manthorpe and Lockley, 2013), thereby resulting in better qualitative analysis and the precision of phytochemical quantitative analysis (Hess, 2007). Hierarchical cluster analysis (HCA) was used to differentiate between a number of chamomile oil samples based on their comprehensive similarity (Khattab *et al.*, 2010).

Reported quality issues of herbal products

A large spectrum of chemical methods, single or hyphenated, from targeted quantitative determination of one marker compound to untargeted multivariate analysis, have been successfully used to reveal different quality issues of many types of commercial herbal products from the global market.

By far, the vast majority of the reviewed articles have reported widely, large, quantitative variations and qualitative differences among the analyzed products. The contents of different analytes differed significantly among TCM products (Duan *et al.*, 2019), the quercetin content in

"carqueja" Brasilian traditional products (Beltrame *et al.*, 2009), some active components in Echinacea products (Osowski *et al.*, 2000), hydroxycitric acid in Garcinia products (Seethapathy *et al.*, 2018b), flavonoids content in St. John's Wort tablets and capsules (Rasmussen *et al.*, 2006), total content of polyphenols, flavonols and phenolic acids in German chamomile tea products (Raal *et al.*, 2012), rutin content, terpenoids in ginkgo products (Dubber and Kanfer, 2004), flavonol, ginkgolide (Dubber and Kanfer, 2006), and partenolide content in feverfew products (Heptinstall *et al.*, 1992), some flavonoids content in skullcap products (Gao *et al.*, 2008), alkaloid content in Ephedra products (Gurley, 1998; Baker *et al.*, 2003), ginsenoside and eleutheroside content in ginseng products (Harkey *et al.*, 2001), silymarin content in milk thistle products (Fenclova *et al.*, 2019), lactic and acetic acid in *Aloe vera* products (Jiao *et al.*, 2010), monacolin K in red yeasts rice products (Avula *et al.*, 2014), fatty acids content in saw palmetto products (Booker *et al.*, 2014), hydrastine and berberine content in goldenseal products (Abourashed and Khan, 2001), yohimbine and ajmalicine content in yohimbine products (Lucas *et al.*, 2015), as well as the phenolic content of cranberry products (Sánchez-Patán *et al.*, 2012). These large compositional variations were due to faults in the production processes, absence of quality control (Beltrame *et al.*, 2009) of the plant raw material (Dias *et al.*, 2013), use of different extraction methods (Seethapathy *et al.*, 2018b), and lack of standardization for quality assurance (Harkey *et al.*, 2001; Sánchez-Patán *et al.*, 2012; Boudesocque-Delaye *et al.*, 2018). Additionally, quite a few other reports, when have compared with the labeled or expected contents, have reported lower content of o-hydroxycinnamic acid derivate in Brazilian "chapeu-de-cuoro" products, naringin in Fructus Aurantii Immaturus products (Xu *et al.*, 2010), various marker compounds in a TCM product (Yao *et al.*, 2016), hypericin in St. John Wort products (Scotti *et al.*, 2019), anisaldehyde in sweet fennel tea products (Bilia *et al.*, 2002), peimine and

peiminine in Fritillariae Thunbergii Bulbus products (Lin *et al.*, 2015), bilobalide in ginkgo products (Kressmann *et al.*, 2002), or hydrastine in goldenseal products (Wang *et al.*, 2001) but also higher than expected content of the total flavonoids and ginkgolides in ginkgo products (Ömür Demirezer *et al.*, 2014), synephrine, octopamine and hordenine in bitter orange-containing products, flavone glycosides, terpene lactones, ginkgolic acids in gingko products (Kressmann *et al.*, 2002), and berberine in goldenseal products (Govindan and Govindan, 2000). Yet, the chemical methods were also able to detect the total absence, or presence below the limit of detection, of important marker compounds such as naringin from Fructus Aurantii Immaturus products (Xu *et al.*, 2010), proanthocyanidin A2 from cranberry products (Boudesocque-Delaye *et al.*, 2018), hidroxycitric lactone from Garcinia products (Seethapathy *et al.*, 2018b), volatile constituents from sweet fennel tea products (Bilia *et al.*, 2002), baicalin from skullcap products (Gao *et al.*, 2008), ephedra alkaloids from ephedra products (Gurley *et al.*, 2000), flavan-3-ols from cranberry products (Sánchez-Patán *et al.*, 2012), or hydrastine from goldenseal products (Govindan and Govindan, 2000). Apart from the inter-product extreme quantitative and qualitative variations, several reports have also detected inter-batch quality variations of St. John's Wort (Wurglics *et al.*, 2001; Farag and Wessjohann, 2012), Scutellaria baicalensis (Ye *et al.*, 2004), or milk thistle (Fenclova *et al.*, 2019) commercial samples. Apart from not containing the labeled quantities or percentages of the marker compounds, some were also outside of the values recognized and recommended by pharmacopeias (Alvarenga *et al.*, 2009; Lin *et al.*, 2015). Unfortunately, even more unexpected modifications of the chemical composition were reported, such as the fortification of *Acacia rigidula* (Pawar *et al.*, 2014) and ginkgo products (Ding *et al.*, 2006), and the presence of undesirable substances, such as ginkgolic acid in ginkgo products, which should not be tolerated for safety reasons (López-Gutiérrez *et al.*, 2016).

The presence of the low or largely variable herbal products on the global market contributes to variances in the pharmacologic actions (Schmidt *et al.*, 2008), and alteration of their expected and claimed therapeutic effects (Sharma *et al.*, 2015; Duan *et al.*, 2019). Furthermore, the differences reported, which leads to different quality of various products in term of their action, may explain ambiguous or non-reproducible results often shown in pre-clinical or clinical trials with herbal medicines (Rasmussen *et al.*, 2006; Schmidt *et al.*, 2008; Farag and Wessjohann, 2012; Boudesocque-Delaye *et al.*, 2018).

Conclusions

The claimed or expected health benefits of the herbal products depends on their quality. Irrespective of their jurisdiction, marketing name or presentation form, traditional medicines and food supplements are herbal preparations with numerous chemical compounds in complex matrices. Several reports have analyzed the chemical composition of a substantial number of commercial herbal products with respect to the labeled ingredients. A wide range of methods were used, from simpler, quicker and cost-effective TLC, HPTLC or HPLC to hyphenated methods with MS or NMR which ensure higher analytical capacity and resolution. Additionally, most of the methods have been coupled with chemometric tools, such as PCA, or PDA, for the multivariate analysis of the high amount of data generated by chromatograms, electropherograms or spectra. The chemical methods have revealed the widespread presence of low or variable quality herbal products in the marketplace. The majority of products present large, qualitative and quantitative, inter-product variations of their chemical composition, ranging from missing markers to strikingly and unnatural high concentrations of some compounds. Moreover, the inter-batch quality variations were frequently reported, as well as the presence of some undesirable substances. The chemical analysis of herbal products is a vital component to raise

the overall awareness of quality in the herbal market and help to generate a more quality driven approach. A focus on high quality, standardization and reproducibility will help manufacturers develop a better reputation with regulators and the general public and produce products that are better placed to achieve their intended effectiveness.

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Declaration of interest

The authors report there are no competing interests to declare.

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Table 1. Quality issues reported after the chemical assessment of commercial herbal products

No. crt.	Country or continent	Products / source / ingredient species	Products (no.)	Quality issues reported	Additional quality issues / observations / recommendations	Chemical method / markers used	Botanical or chemical reference materials / standards	Reference
1	Brazil	"carqueja" products / herbal shops, pharmacies / *Baccharis trimera*	12	large variations in the percentage of flavonoids (quercetin)	the irregularities observed are probably due to faults in the production process and absence of quality control	TLC / 3-o-methyl-quercetin	*B. trimera* reference samples / Brazilian Pharmacopoeia	(Beltrame *et al.*, 2009)
2	Brazil	"guaco" products (leaves, tinctures) / market, pharmacies / *Mikania glomerata*	6	inconsistency between the concentration of the tincture and the coumarin content	the analyzed samples showed one or more of the evaluated parameters outside of the values recognized by the Brazilian Pharmacopoeia	TLC, RP-HPLC / quantification of coumarin (1,2-benzopyran)	standard vegetable drug (collected *M. glomerata* sp.) / chemical reference standards	(Alvarenga *et al.*, 2009)
3	Brazil	"chapéu-de-couro" herbal products (raw material) / different suppliers / *Echinodorus grandiflorus*	3	o-hydroxycinnamic acid derivative exhibited content lower than the recommended minimum	highlight need to carry out quality control of plant raw materials	TLC / caffeic acid, isoorientin, swertiajaponin, o-hydroxycinnamic acid derivatives	Brazilian Pharmacopoeia	(Dias *et al.*, 2013)
4	China	"zhish" (Fructus Aurantii Immaturus) products / drug stores, markets, manufacturers / *Citrus aurantium*	26	striking concentration disparity of naringin and hesperidin in herbal materials; in some samples naringin had not been detected or it could not be accurately quantitated	the quantitation standards of the two compounds should be instituted by correlative institutions as soon as possible	HPLC-DAD/ PCA/ HAD/ SA / hesperidin, naringin	authenticated samples of Fructus Aurantii Immaturus / chemical reference standards	(Xu *et al.*, 2010)

5	China	batches of "Wu Ji Bai Feng Pill" (water-honeyed pills, big honeyed pills, tablets) / manufactures / fourteen herbal materials and six animal crude materials	19	the contents of the analytes differed significantly among different products and might depend on the raw materials, dosage forms as well as processing procedures	the observed variations might lead to variances in the pharmacologic actions, even their therapeutic effects	UHPLC–MS/MS/ PCA/ HCA / quality markers	chemical reference standards	(Duan *et al.*, 2019)
6	China	batches of "Shuxiong Tablet" / drugstores, manufacturers / *Panax notoginseng, Carthamus tinctorius, Ligusticum striatum*	12	low content of some markers	quality differences possibly caused by different preparation process or use of poor-quality drug materials	UPLC/QTOF - Fast DDA/ 39 saponins, 5 QCGs, 17 FOGs, 7 phenolic acids, 4 phthalide derivatives	in-house SXT standard preparation from crude drug reference materials (Notoginseng Radix et Rhizoma, Carthami Flos, Chuanxiong Rhizoma) / chemical reference standards	(Yao *et al.*, 2016)
7	China	St. John's Wort products (loose material) / herbal markets, pharmacies and producer's cultivation / *Hypericum perforatum*	5	the hypericin content was found to be low in commercial material, either due to higher content of woody material, or unknown age of the sample	unregulated products' significant variation in composition is very heavily influenced by the various processing techniques of the *materia prima*	^{1}H-NMR/ PCA, HPTLC / avicularin, guaiaverin, rutin, hypericin	authenticated Hypericum sp. samples, St. John's Wort reference dry extract / chemical reference standards	(Scotti *et al.*, 2019)
	Bulgaria		2					
	Greece		2					
	Chile		1					
	UK		1					
8	Denmark	St. John's Wort products (tablets, capsules) / commercial suppliers / *Hypericum perforatum*	10	considerable differences in the products composition (e.g., flavonoids), inter-product and inter-batch variation	the differences observed may cause different quality of the products in term of their action, and may explain ambiguous results often shown in clinical trials with herbal medicines	^{1}H-NMR/ PCA	n/a	(Rasmussen *et al.*, 2006)
9	Egypt	chamomile oil products / local market / *Matricaria chamomilla*	2	inferior quality grade oil	non-trusted suppliers which are marketing inferior quality oils	DE-TLC/ HCA, GC/ HCA / essential oil	chamomile oil sample produced in laboratory, different chamomile oil	(Khattab *et al.*, 2010)

							samples collected from local manufacturers	
10	Estonia	German chamomile products (teas) / food markets, retail pharmacies / *Chamomilla recutita*	12	the total content of polyphenols showed a significant variability as well as content of total flavonols and total phenolic acids	the quality of the commercial chamomile teas was very variable, and the chamomile teas available in pharmacies should be preferred for the medical purposes	GC-MS, LC-DAD–MS/MS / essential oil, terpenoids, polyphenols	commercial chemical standards	(Raal *et al.*, 2012)
	USA		1					
11	Europe	St. John's Wort products (tablets, capsules) / retail stores / *Hypericum perforatum*	12	differences between various preparations in terms of flavonoid content	differences in sample composition may influence the pharmacological activity of preparations and may explain differences in outcomes of clinical trials	HPLC-PDA-SPE-NMR-MS / oligomeric proanthocyanidins	chemical reference standards	(Schmidt *et al.*, 2008)
	North America		8					
	Africa		2					
	Asia		2					
12	France	cranberry products (stick powder, powder capsules, tablets, syrups) / pharmaceutical market / *Vaccinium macrocarpon*	10	dramatic disparity between products (PACs profile), absence of PAC-A2, poor quality of polyphenol ingredients	the analyses highlighted the plural PAC composition of commercial products and the lack of standardization for cranberry-based products on the market, explaining the non-reproducibility of clinical trials	BL-DMAC, HPTLC-densitometry / epicatechin, PAC-A2, PAC-B2, PAC-A2, epicatechin ratio	commercial pasteurized and clarified raw cranberry juice / chemical reference standards	(Boudesocque-Delaye *et al.*, 2018)
13	Germany	Echinacea products (root, herb, whole plant) (homeopathic mother tincture, pressed juice, tablets, spagyric tincture) / pharmacies, manufacturers / *Echinacea angustifolia, E. pallida, E. purpure*a	25	large differences of active components between comparable drugs of different manufacturers and between different charges of the same remedy	the concentration of both active components varied extremely depending on the type of remedy, on the Echinacea-species and on the part of the plant; preclinical and clinical studies should always include the quantification of the potentially active components	HPLC / cichoric acid, Dodeca 2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide (alkamides 8,9)	chemical reference standards	(Osowski *et al.*, 2000)

14	Germany	St. John's Wort products (capsules, film-coated tablets, sugar-coated tablet) / manufacturers, pharmacies / *Hypericum perforatum*	8	widely differing amounts of hypericin and hyperforin, pronounced interbatch variability	preparations studied exhibited large differences in hypericin and hyperforin content and are not interchangeable for the treatment of mild-to-moderate depression	HPLC, polarography / hyperforin; total hypericin	chemical reference standards	(Wurglics *et al.*, 2001)
15	Germany	St. John's Wort products (tablets, capsule) / retail stores / *Hypericum perforatum*	5	variable quality, particularly in hyperforins and fatty acid content, including between batches from the same supplier	differences in content of hyperforins may well contribute for inconsistent results in clinical trials	UPLC-qTOF-MS/ PCA / hyperforins, catechins, aphthodianthrones, flavonoids, fatty acids, phenolic acid	collected material (flowers) from authenticated *H. perforatum* plant / chemical reference standards	(Farag and Wessjohann, 2012)
	Egypt		4					
16	India	Triphala products (powder) / retailers, herbal practitioners / *Phyllanthus emblica, Terminalia bellirica, T. chebula*	20	significant difference of the concentration of quantified metabolites was observed between brands and samples of the same brands	a large variation in concentration of therapeutically important phytochemicals may result in alteration in efficacy	gravimetric determination, titrimetric method / total phenolic, tannin, ascorbic acid	Triphala powder samples, standard Triphala powder	(Sharma *et al.*, 2015)
17	India	Garcinia products (capsules, tablets) / pharmacies, internet / *Garcinia gummi-gutta, G. indica*	5	large variation in the content of hydroxycitric acid; only one product contained quantifiable amounts of hydroxycitric acid lactone	the absence of (−)-hydroxycitric acid lactone in the supplements with Garcinia extracts might be due to the extraction method employed	^{1}H NMR / (−)-hydroxycitric acid, (−)-hydroxycitric acid lactone	authenticated BRM from eleven species of *Garcinia* L.	(Seethapathy *et al.*, 2018b)
	Norway		1					
	Romania		1					
	Sweden		1					
	USA		2					
18	Italy	sweet fennel pre-packaged tea bags and instant tea products (freeze-dried powders) / local pharmacies, grocery stores / *Foeniculum vulgare*	5	variable chemical composition (fenchone in lower amounts, anisaldehyde in traces, no volatile constituents)	possible presence of bitter fennel or, for the powdered material, the presence of other parts of fennel	GC–MS / transanethole, p-anisaldehyde, limonene, fenchone, camphor, methylchavicol, a-	commercial reference samples of fruits of *F. vulgare* / chemical reference standards	(Bilia *et al.*, 2002)

						terpineol, carvone, andeugenol		
19	South Africa	ginkgo products (solid oral dosage forms-tablets, capsules, herbal extract-gelatin capsule) / local pharmacy / *Ginkgo biloba*	5	average marker content varied markable (e.g., 25-fold difference in the content of rutin)	suitable quality control measures need to be implemented to ensure the quality, safety and efficacy of commercially available Ginkgo biloba products	HPLC/ PDA / rutin, quercitrin, quercetin, kaempferol, isorhamnetin	chemical reference standards	(Dubber and Kanfer, 2004)
10	South Africa	ginkgo products (solid oral dosage forms-tablets, pulverized leaf extract -hard gelatine capsule) / local pharmacy / *Ginkgo biloba*	6	large discrepancies occurred in both the flavonol and ginkgolide marker content, an 11-fold difference in the amount of rutin present between two products	major discrepancies in the marker content between products	RF-MEKC / 2 flavonol glycosides, 3 flavonol aglycones, 4 terpene trilactones, 1 sesquiterpene; quantification of rutin, quercetin	chemical reference standards	(Dubber and Kanfer, 2006)
21	South Korea	"Ojeok-san" products (granules) / pharmaceutical companies / Atractylodis rhizoma, Ephedrae herba, Citri Unshius pericarpium, Magnoliae cortex, Platycodonis radix, Aurantii Fructus immaturus, Angelicae gigantis radix, Zingiberis rhizoma, Paeoniae radix, Poria sclerotium, Angelicae dahuricae radix, Cnidii rhizoma, Pinelliae tuber, Cinnamomi cortex, Glycyrrhizae radix et rhizoma, Zingiberis	9	lack of one or more compounds (protocatechuic acid, chlorogenic acid, ferulic acid, nodakenin, hesperidin, neohesperidin, cinnamaldehyde) while the water extract and commercial granules of OJS were not chemically equivalent	low correlation between the OJS samples, particularly the laboratory produced water extract and the commercial granules, can presumably be ascribed to the different ratios of the compositional herbal medicines, herbal resources, or extraction procedures of the OJS preparations between different pharmaceutical companies.	HPLC/ PCA/HCA/ gallic acid, protocatechuic acid, chlorogenic acid, albiflorin, paeoniflorin, ferulic acid, liquiritin, benzoic acid, nodakenin, hesperidin, naringin, neohesperidin, ononin, oxypeucedanin hydrate, cinnamic acid, byakangelicin, cinnamaldehyde, benzoylpaeoniflorin, glycyrrhizin	dried herbal drugs consisting of OJS / chemical reference standards	(Kim *et al.*, 2015)

		rhizoma recens, Allii fistulosi bulbus						
22	Spain	ginkgo products (capsules, tablets) / local markets / *Ginkgo biloba*	8	the amount of terpenoids greatly varies among samples and presence of undesirable substances (e.g., ginkgolic acid)	great variability among the content obtained and product labels, which contain unclear and minimal information (as the presence of isoflavonoids, which can provoke negative effects in certain type of people)	UHPLC-Orbitrap-MS / flavanols, flavanones, flavones, isoflavonoids, phenolic acids	in house-made polyphenols database / phytochemical commercial standards	(López-Gutiérrez *et al.*, 2016)
	Poland		3					
23	Taiwan	herbal materials of Fritillariae Thunbergii Bulbus / local markets / *Fritillaria thunbergii*	10	product with low total content of peimine and peiminine	according to the specification in Chinese Pharmacopeia that the total content of peimine and peiminine should be not less than 0.080%, a sample was an unqualified herb that could not be used clinically	HPLC-UV/ HCA/ peimine, peiminine	chemical reference standards	(Lin *et al.*, 2015)
24	Taiwan	5:1 concentrated extract products (prepared from dried roots) from different companies / *Scutellaria baicalensis*	6	significant product-to-product and batch-to-batch variation of the marker compounds (e.g., no baicalin at all and baicalein concentration 0-52.3 g/mg)	due to significant variation in chemical composition and biological activities of the commercial extracts, the amount of marker components may not reflect biological activity levels	HPLC / baicalin, baicalein	chemical reference standards	(Ye *et al.*, 2004)
	China		4					
25	Turkey	ginkgo products (extracts) / local pharmacy, local markets / *Ginkgo biloba*	13	total flavonoids and ginkgolides higher in medicinal products, no or very little flavonoids in food supplements	the chemical profiling of herbal medicinal products from pharmacies are quite different than samples obtained from different supplement manufacturer	LC-MS, HPLC-DAD / ginkgolides, flavonoid aglycones	reference standards purchased, isolated, prepared by acidic hydrolysis)	(Ömür Demirezer *et al.*, 2014)

26	UK	feverfew products (powder, leaf, capsules, tablets) / *Tanacetum parthenium*	33	in some products parthenolide content varied widely and in some products was not detected	since therapeutic efficacy has only been demonstrated for preparations of feverfew that contain parthenolide, it is suggested that manufacturers of feverfew products should use measurements of parthenolide as a means of standardization and quality control	HPLC, ^{1}H-NMR / parthenolide	authenticated *T. parfhenium* material (leaf, powder, seeds, capsule) / chemical reference standards	(Heptinstall *et al.*, 1992)
27	UK	feverfew products (tablets) / *Tanacetum parthenium*	14	the spectrum of some samples resembles that of a single component (tentatively identified as mannitol) rather than a multi-component extract	inter-batch variability was identified	^{1}H-NMR/ PCA	n/a	(Bailey *et al.*, 2002)
28	UK	skullcap products (tinctures) / different companies / *Scutellaria lateriflora, S. baicalensis*	11	wide variability in biomarker concentrations between products (including the absence of baicalin from some products)	quality differences between commercial tinctures have important implications for the manufacturers, practitioners, and pharmacology and clinical researchers	HPLC / flavonoids (baicalin, baicalein, wogonin)	chemical reference standards	(Gao *et al.*, 2008)
29	UK	ginkgo products (tablets, capsules, pure extract) / local market, nationwide health food shop, manufacturer / *Ginkgo biloba*	5	samples possible fortified by low-grade quercetin or rutin additions	remarkable variations in the rutin, quercetin and terpene lactone contents	RP-HPLC/ ESI-MS / bilobalide, ginkgolides A, B, C, quercetin, kaempferol, isorhamnetin, rutin hydrate, quercetin-3-b-D-glucoside, quercitrin hydrate	chemical reference standards	(Ding *et al.*, 2006)

30	USA	bitter orange-containing products (tablets, capsules, gel-containing capsules, drink powders) / internet / *Citrus aurantium*	59	many of these supplements contain elevated levels of synephrine, octopamine and hordenine	very few products appear to meet claims for their label concentration declarations	LC–MS/MS / phenethylamines (synephrine, octopamine, tyramine, N-methyltyramine, hordenine)	chemical reference standards	(Pawar *et al.*, 2020)
31	USA	"ma-huang" products / retail outlets, internet / *Ephedra* sp.	47	large variations existed in individual alkaloid content within and between product lines	investigation of information on product labels revealed large variations in recommended and maximum doses of the ephedra alkaloids	GC/MS / alkaloids	chemical reference standards	(Baker *et al.*, 2003)
32	USA	ginkgo products (tablets, capsules, caplet) / health food stores, supermarkets / *Ginkgo biloba*	27	the concentrations of flavone glycosides, terpene lactones, ginkgolic acids were above the specification whereas the contents of bilobalide were too low	the considerably high amounts of ginkgolic acids found should not be tolerated for safety reasons	HPLC / flavone glycosides, terpene lactones, ginkgolic acids	EGb 761 extract / chemical reference standards	(Kressmann *et al.*, 2002)
33	USA	ginseng products (powders, capsules) from the genera *Panax* or *Eleutherococcus* / local health food store / *P. ginseng, P. quinquefolius, P. notoginseng, Eleutherococcus senticosus*	25	concentrations of marker compounds differed significantly from labeled amounts and there was also significant product-to-product variability (ginsenosides 15- and 36-fold and concentrations of eleutherosides 43- and 200-fold) in capsules and liquids	variability in concentrations of marker compounds suggests that standardization may be necessary for quality assurance	LC-MS/MS, HPLC / ginsenoside, eleutheroside	chemical reference standards	(Harkey *et al.*, 2001))

34	USA	*Acacia rigidula*-containing products (tablets, capsules) / internet / *Acacia rigidula*	21	significant differences in the amine profiles of authenticated plant material and dietary supplements	given the low natural abundance of PEA in the plant materials, it appears nearly impossible to achieve the amounts of PEA found in the dietary supplements by formulating them with plant material or extracts of *A. rigidula*	LC–MS/MS, GC–MS / biogenic amines (phenethylamine, tyramine and tryptamine derivatives)	*A. rigidula* (collected or purchased) authenticated plant material (fresh leaves, twigs, bark) / chemical reference standards	(Pawar *et al.*, 2014)
35	USA	ephedra-containing supplements (tablets, hard gelatin capsules, soft-gelatin capsules, liquid extract) / local retailers, internet / *Ephedra* sp.	20	discrepancies between the label claim for ephedra alkaloid content and actual alkaloid content in excess of 20% or devoid of ephedra alkaloids	excessive lot-to-lot variability	HPLC / ephedrine-type alkaloids (ephedrine, pseudoephedrine, methylephedrine, norephedrine, norpseudoephedrine)	chemical reference standards	(Gurley *et al.*, 2000)
36	USA	milk thistle products (capsules with dried, oil-based extracts) / market / *Silybum marianum*	19	large differences in the silymarin content, as well as substantial inter-batch differences	marked differences in the content of individual flavonoids/ flavonolignans, even within different batches by the same manufacturers	U-HPLC-HRMS / total quantitative isolation of silymarin flavonoids/ flavonolignans	reference dried milk thistle extract / chemical reference standards	(Fenclova *et al.*, 2019)
	Czech Republic		7					
37	USA	*Aloe vera* products (whole leaf or gel freeze-dried powder, whole leaf spread dried powder, gel dehydrated powder, gel powder) / *Aloe vera*	18	significant differences among *A. vera* products were observed for the contents of lactic acid and acetic acid	the differences among products indicates possible microbial contamination and deacetylation in manufacture and storage	^{1}H-NMR / nicotinamide	authenticated *A. vera* samples (inner leaf powder, decolorized whole leaf freezing dried powder) / Aloe acetylated polysaccharides reference standard	(Jiao *et al.*, 2010)
38	USA	red yeast rice (RYR) - containing products / online / *Monascus purpureus* - fermented rice	14	large variations (20-40-fold) in quantity and quality of monacolin K	the quality of commercial products was also variable in respect to ratio of MK:MKA as well as dehydromonacolin K and citrinin content	UHPLC–DAD–QToF-MS/ PCA / monacolins, citrinin	RYR authenticated samples / chemical reference standards	(Avula *et al.*, 2014)
39	USA		13					

	UK	saw palmetto products (soft and hard gel capsules, tablets, tinctures) / retail outlets, pharmacies / *Serenoa repens*	11	the fatty acids varied widely with a factor of about 177 between the minimum and maximum concentration	inaccurate labeling of fatty acid content	GC, ^{1}H-NMR/ PCA / quantification of nine fatty acids	chemical reference standards	(Booker *et al.*, 2014)
	Canada		7					
	Netherlands		7					
	Switzerland		6					
	Spain		5					
	South Korea		4					
	Finland		1					
	Germany		1					
40	USA	goldenseal products (capsules, raw, tea bag, liquid extract) / local retailers, internet / *Hydrastis canadensis*	12	wide range of content variation for hydrastine (0.00-2.51%) and berberine (0.00-4.35%)	wide range of alkaloid concentrations implies that goldenseal products need to conform to common acceptable quality control criteria	HPLC / hydrastine, berberine	authenticated crude goldenseal powder / chemical reference standards	(Abourashed and Khan, 2001)
41	USA	yohimbine products (powders, gel caps, tablets) / local dietary supplement stores / *Pausinystalia johimbe*	10	a wide range of yohimbine and ajmalicine ranging from not detected to three times the specified amount on the label of yohimbine	other incurred samples were quantified at low ppb levels to the actual level specified on the label	LC/QTOF-MS / indole alkaloids	authenticated yohimbe bark and extract / chemical reference standards	(Lucas *et al.*, 2015)
42	USA	"ma-huang" products / local retailers, internet / *Ephedra sinica*	9	considerable variability in alkaloid content (EPH 1.08-13.54 mg) and lot-to-lot variations in EPH of 137%	EPH content is not a label requirement for Ephedra-containing supplements therefore less stringent labeling requirements may contribute to toxicity associated with these products	HPLC / ephedrine-type alkaloids	unprocessed *E. rhytidosperma* / chemical reference standards	(Gurley, 1998)
43	USA	cranberry products (powder capsules, gel capsules, pills, loose powders, syrups) / *Vaccinium macrocarpon*	9	wide differences in their phenolic content and distribution, including products completely devoid of flavan-3-ols to highly purified	lack of product standardization and incongruence between global and individual compound analysis	UPLC-DAD-ESI-TQ MS/ PCA / phenolic acids, flavan-3-ols, anthocyanins; total polyphenols	chemical reference standards	(Sánchez-Patán *et al.*, 2012)
	UK		4					
	Belgium		2					
	Spain		2					
	China		1					

	France		1	ones, either in A-type proanthocyanidins (PACs) or in anthocyanins				
44	USA	goldenseal products (capsules, tablets) / local retailers / *Hydrastis canadensis*	5	quite a lot of samples only contained berberine or the concentrations of hydrastine were very low	contents of alkaloids are different from products to products covering a range of 1.25 mg to 57 mg total alkaloid per serve	HPLC / hydrastine, berberine	reference goldenseal (roots and herbs) from commercial suppliers / chemical reference standards	(Wang *et al.*, 2001)
45	USA	ginkgo products (capsules) products / local pharmacy, health food stores / *Ginkgo biloba*	6	a great deal of variation in the content of the chemical markers in each capsule	this is most likely due to the fact that standard GBE sets a minimal amount for the total ginkgolides (>6%) and flavonoids (>24%) and doesn't indicate the actual concentrations	GC-MS / bilobalide, ginkgolides A, B, C, kaempferol, quercetin, isorhamnetin	standardized *G. biloba* extract / chemical reference standards	(Deng and Zito, 2003)
46	USA	goldenseal products (capsules containing fine powder) / *Hydrastis canadensis*	2	did not show any hydrastine but had larger amounts of berberine	TLC is a viable method but HPLC remains the best available method for the quantitative estimation of the active alkaloid content of goldenseal products	TLC, HPLC / hydrastine, hydrastinine, berberine	authenticated goldenseal samples (bulk powdered or coarsely chopped material) / chemical reference standards	(Govindan and Govindan, 2000)
	Total		**727**					

Table 2. Chemically assessed herbal products at continental level

No. crt.	Continent	Products (no.)
1	North America	334
2	Europe	216
3	Asia	136
4	South America	22
5	Africa	19

Table 2. Chemically assessed herbal products at national level

No. crt.	Country	Products (no.)
1	USA	319
2	UK	79
3	China	67
4	Germany	39
5	India	25
6	Brazil	21
7	Taiwan	16
8	Spain	15
9	South Korea	13
10	Turkey	13
11	Estonia	12
12	France	11
13	South Africa	11
14	Denmark	10
15	Canada	7
16	Czech Republic	7
17	Netherlands	7
18	Egypt	6
19	Switzerland	6
20	Italy	5
21	Poland	3
22	Belgium	2
23	Bulgaria	2
24	Greece	2
25	Chile	1
26	Finland	1
27	Norway	1
28	Romania	1
29	Sweden	1