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A Concise Review on Quality Control of Herbal Medicines

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Abstract

Quality control of botanical products, including herbal raw materials, herbal extracts and herbal medicines, remains a challenge. Traditional qualitative (eg. identification and chromatographic profiles) Most plant materials, plant extracts, and medicinal herbs cannot be guaranteed for quality based solely on the content or presence/absence of a single (sometimes randomly selected) compound. In this regard, sample-centric approaches have been extensively explored by introducing the use of multivariate data analysis in chromatography/spectroscopy studies. Herbal medicine, especially those from traditional Chinese or Indian medicine, is becoming increasingly popular in Europe and America. Their use is often based on long-term historical use rather than scientific evidence. Therefore, analytical tools to ensure efficiency, safety and consistency are in high demand. This review assesses the importance of the EC for quality control of herbal medicines over the past five years. Since the area ratios of the two characteristic peaks are almost identical, even though the areas are different for the same plant, the present article provides an additional method for discriminating herbal medicines. PCA groups herbal drugs into different groups, which clearly show that this method can adequately discriminate different herbal drugs using FTIR data. The levels of toxic heavy metals (Cd, Pb, Cr and As) were measured and the results were compared with the World Health Organization (WHO) recommended upper daily limit for heavy metals.

Keywords: Quality Control, Herbal Medicine, FTIR, WHO.

Introduction

Traditional medicinal herbs (THM) and their preparations have been used for thousands of years in many oriental countries such as China, Korea and Japan. Available as individual herbs or combinations of herbs in complex formulas extracted with boiling water during the brewing process. This is probably the main reason why quality control for Oriental medicine is more difficult than for Western medicine.

Typically, one or two markers or pharmacologically active ingredients in herbs and/or herbal mixtures are used to assess the quality and authenticity of current herbal medicines, to identify individual herbs or HM preparations, and to estimate the quantitative plant content of plants and plant products. However, this type of identification usually does not give a complete picture of an herbal product, since several components are responsible for its therapeutic effect. These different components can act "synergistically" and are difficult to separate into active parts. In addition, the chemical

composition of the constituent herbs in HM products may vary depending on the season of harvest, the origin of the plant, the drying process, and other factors[1, 2, 3]. A major problem with compound-based approaches is that therapeutic actions based on one or more compounds cannot be elucidated for most plant species. Therefore, it is inappropriate to judge efficacy and safety by content alone. This becomes an even bigger problem when considering combinations of this review is a general assessment of PM/PE/HM quality management. Traditional approaches are considered, but we focus on using multivariate methods. Two main aspects of Pharmacopoeial testing are considered: identification (qualitative analysis) and analysis (quantitative analysis). Other related topics such as pharmacological testing for HM stability and quality control are also covered. For clarity, in this review different herb, such as in TCM.HM is the standard term for finished products (e.g., tinctures, pills, tablets). For raw materials such as plant parts, "plant materials" (PM) are used and "plant extracts" (PE), extracts of plant origin and other processed APIs such as fractions and concentrated extracts.

Need of Quality Control

Herbal quality control is more important to maintain the quality of herbs and natural products. In terms of quality control, identify content, counterfeits and substitutes; purity of materials; the identification of the most important active chemical constituents of a particular plant, called the Pharmacopoeial aspect of quality control. Standardization is the process of measuring the qualitative and quantitative values of medicinal plants according to established criteria and parameters. Based on various important evaluation parameters such as organoleptic properties, ash value, moisture content, microbial contamination, chromatographic and spectroscopic evaluation, WHO prepares guidelines for standardization methods and procedures for standardization of herbal medicines along with current trends and future. The quantitative composition of these components varies according to soil and environmental conditions. So, it can vary from place to place. Exceeding certain limits of these components can lead to various health problem. Traditionally, the quality of herbswas determined by skilled herbalists based on differences in plant appearance. Recently, various chromatography techniques such as high-performance liquid chromatography (HPLC), gas chromatography (GC) and thin layer chromatography (TLC) have been developed. These methods are accurate but require laborious and time-consuming sample preparation steps. Therefore, there is a need to develop a rapid, simple and accurate analytical method for the identification and quality assessment of herbal medicines.2004 China Food and Drug Administration (SFDA) controls the fluid injection configuration. HM ingredients according to strict quality procedures Such as chemical analysis and standardization. Footprint for this, HM fluid injection is essential. the various experimental techniques, Therefore, chromatographic methods are highly recommended. To obtain the fingerprints of these products [4-14].

Authentication/Qualitative Analysis

1. Botanical method

It is estimated that there are more than 390,000 plant species and about 1,100,000 scientific names worldwide [15]. More than 28,000 plant species have been recorded, some used for medicinal purposes [16]. Scientific naming conventions for plant species have changed over time [17,18,19,20]. Recently, with the development of knowledge about the phylogenetic relationships between plant species, changes to the nomenclature have been proposed [21]. Difficulties in plant identification can arise from the wide range of phenotypic variation. This variation occurs between different populations of the same species [21] or within individuals [22]. One of the most notable changes in the leaves because the leaves can accept full sun or shade.

Taxonomic analysis is fundamental, as is the cataloging of herbarium specimens [23]. Sometimes other anatomical features such as trichomes type [24], cork layer [25] or stomatal type can be used to ensure plant identification [26]. However, most of these analyzes are integrative and suggest better live models. Anatomical analysis can be performed with the rehydrated material if necessary. In all cases, samples are processed on a microtome or hand section, mounted on slides and then analyzed according to standard protocols [27]. Special dyes such as Astra blue, toluidine blue, safranin, or Lugol's are often used to stain specific cells. However, morphological analysis does not always guarantee accurate identification and species identification can be attempted.

2. Chemical method

The evaluation of the chemical composition complements the traditional methods of plant identification [28]. It not only shows the identity of plant species but also helps to describe cultivars, varieties and subspecies variants such as chemo types [28]. Chemical composition also reflects the production process of PE and HM, especially the extraction step that plays a decisive role in the final composition of those materials [29, 28].In addition to the certification of raw materials, adequate monitoring of the constituent profile of PM/PE/HM is important to ensure the consistency of the therapeutic profile.

Sample preparation

Preparation of a sample preparation is one of the most important steps in the quality control of botanical products. It focuses on the extraction process and aims to recover analytes from plant tissues so that they can be used for chemical analysis [30]. This is stated in the statement of Choi and Verpoort [31]. Traditionally, maceration, decoction and infusion methods are used. However, over the years, added heat and improved extraction methods have accelerated and improved the extraction process (e.g., reflux, Soxhlet extraction) [32]. Currently, various other energy sources such as acoustic waves (UAE), microwaves (MAE) and pressure (PSE) are used to improve the extraction procedures [33]. These state-of-the-art methods improve analyte recovery and extraction reproducibility, generally reducing time and solvent consumption [32, 34]. Purification procedures such as LLE and SPE should also be considered to focus markers and remove

interferences [34]. This step is generally avoided, but in some special cases (e.g., low analyte concentrations) a purification method must be used. In the reviewed studies (188 articles, Table 1S, Supporting Information), approximately 50% recovered analytes from plant tissue using EAU. For clarity, only quality control studies are included in this section. In general, UAE has been widely used to extract metabolites from botanical sources [35]. However, UAE is known to cause temperature rise and the formation of radical species [34]. Therefore, when targeting known unstable analytes, this technique should be avoided or experimental conditions should be carefully controlled. Methods using pressure (PSE and SFE) accounted for 5% of studies. By controlling factors such as temperature, pressure and solvent viscosity can be lowered and diffusivity increased to improve solvent penetration through the plant material, improving extraction efficiency. Reduction of extraction time and solvent volume are some additional advantages of this approach [34, 36]. Despite their advantages, PSE and SFE are less popular due to their high cost. Regardless of the extraction method, water, hydro alcoholic mixtures (water/ethanol or water/methanol), or alcohols (ethanol or methanol) were mostly used as solvents. These solvents are mainly used for the extraction of NPs, probably due to their polarity, corresponding to that of other classes of secondary metabolites [32]. Less polar solvents are usually used when targeted extraction is required, such as chlorinated solvents for steroid and terpenoid extraction [32, 37]. Solvent properties can also be modified by acidifying agents or alkalis, especially for obtaining alkaloids [38, 39]. This can also help with cleaning techniques. Less than 10% of the studies in this review used purification procedures (e.g., LLE or SPE), with the latter one-third being used for alkaloid extraction. Concentrated fraction. Purification is a post-extraction procedure aimed at enriching an analyte. Two main approaches are used: LLE or SPE. Cleaning is an additional step in sample preparation and is generally avoided for this reason. In general, researchers try to keep the pre-analysis method as simple as possible and focus on the analysis phase of the study [31].The analysis showed that researchers did not put much effort into optimizing sample preparation. Only 7% of studies used some form of extraction optimization. This raises a caveat that extra care must be taken in sample preparation. If NPs are not properly extracted, all subsequent analytical efforts may be compromised, resulting in erroneous content estimates or representative metabolic profiles. This is a recurring problem mentioned in other papers [31, 32, 34]. Also, less than 50% of the optimization studies used the Doe method. Doe is a multivariate approach that simultaneously assesses the influence of several factors on a given response. Compared to the OVAT method, it has the advantage that interaction effects can sometimes be estimated. Due to the good experimental distribution of Doe, the experimental domain can be well mapped in a given number of experiments [34]. The most commonly used Doe method is RSM. A second-order polynomial model is used to predict the best level of the evaluated factor that gives an acceptable or optimal response [34]. More examples of Doe applications can be

found in the reviewed literature. Most of them found suitable conditions using L9 (34) orthogonal lattices [40, 41] or Box-Behnken models [38, 42]. Many analytical studies can benefit from optimizing sample preparation. The extraction method is usually selected based on the researcher's experience. Without validation, it may not provide enough relevant information. A variety of technologies exist and their applications to plant products need to be explored in both academia and industry. In this context, the Doe generally provides a reasonable approach to properly explore areas of experimentation in experimental economic strategies.

Chromatography

A chromatographic profile shows the chemical composition of the sample imaged by the selected detector. This composition mainly depends on the species, plant parts, environmental conditions and extraction methods. Therefore, chromatographic methods have been widely used to identify herbal products and identify known counterfeits [43, 44]. To this end, methods must be able to distinguish plant material from potential additives and substitutes [44], which implies the need to establish a series of plant species-specific markers [45]. In general, accurate species identification depends on monitoring multiple components, and most chromatographic methods are limited in their ability to accommodate these diverse assemblages of analytes [45]. Therefore, a combination of independent methods involving different groups of components is recommended to achieve the desired level of selectivity [46, 45]. Among the chromatographic methods used to monitor phytochemical profiles, TLC is one of the most widely used and is included in most Pharmacopoeial monographs on plant products [47, 44]. This method is known to have several advantages such as ease of analysis and sample preparation. Relatively low-cost ability to process multiple samples in parallel variability of experimental conditions and availability of specific inducing reagents [47, 48]. However, TLC, which is primarily a passive technique, is often less reproducible because its performance is highly dependent on experimental factors (e.g., room temperature, humidity, and saturation) 47.Many of these limitations have been overcome with the development of HPTLC, which uses small particle stationary phases and is typically performed with instruments that can automate sample application, development, and documentation, allowing better standardization of chromatographic conditions to improve reproducibility [47,48]. Additionally, HPTLC applications are not limited to identification testing, as this method is suitable for batch-to-batch consistency assessment, chromatographic profile monitoring during stability studies, and process control during product manufacturing [46, 49].TLC or HPTLC methods must be validated to demonstrate suitability [46, 48, 49]. According to the Basic Guidelines for the Validation of Analytical Procedures [50, 51, 52] identification methods such as qualitative TLC and HPTLC can only be validated by confirming their selectivity and [22] specificity. Therefore, some authors suggested that the robustness and reproducibility of these methods should also be checked [46, 48]. Forced degradation

studies should also be considered for methods used for stability studies [46, 48, 49]. Several interesting approaches for the standardization and validation of HPTLC-based analytical methods were reported by Coll[46] and Reich et al [48].

Types of Chromatography

Thin layer chromatography (TLC)

TLC has many distinct advantages. Determination during the analysis of herbal preparations. Also, TLC It is very simple and can be used for several models. Analyze. More than 30 points with patterns for each plate can be read simultaneously. so, use it TLC is still popular for the analysis of herbal preparations [53-62,63-66].Useful qualitative and quantitative information can be obtained from the developed TLC plates[67] lists four cordyceps specimens. Sinensis, a joint product of Sino-Japanese cooperation, has more valuable medical effects than others. This is because it contains the most effective ingredient, cordycepin. Also, by analyzing and digitizing the image, methodology developed in informatics, assessment similarities between different models are also possible.

Gas Chromatography

Many of the pharmacologically active components of herbal preparations are known to be volatile chemical components. Therefore, the analysis of volatile compounds by gasesis done by Gas Chromatography which is very important in aroma analysis. There are many GC analytes of essential oils. First, MC in volatile oils provides a reasonable “fingerprint” for plant identification, composition and relative concentrations of organic matter. The volatile oil compounds are plant specific and may contain impurities in the volatile oils which need to be identified. Second, the extraction of volatile oils is relatively simple and standardizable components can be easily identified by GC-MS analysis. Relative amounts of ingredients can be used to monitor or evaluate specific properties of herbal preparations. Variations in carrier oil composition may also be used. The advantage of GC is its high detection sensitivity for almost all volatile compounds. This is especially true for traditional FID detection& GC-MS. In addition, the high selectivity of capillaries of the column allows the simultaneous separation of many volatiles in a relatively short time. So, it is mostly used. In recent decades, GC has become a popular and useful analysis tool in research on herbal medicine [53-62]. Specially, using a hyphenated GC-MS instrument, reliable compound identification information is available. But the most significant disadvantage is that it is not useful for analysis of polar and volatile compound samples. For this, you have to use tedious sampling operations which may contain derivatives. Therefore, liquid chromatography is another essential tool that we use.

High Performance Liquid Chromatography (HPLC)

HPLC is a widely used method for herbal analysis. Because it is easy to learn, easy to use and has no limitations. By the volatility or stability of the sample compound. In general, HPLC can be used to analyze almost any compound from herbal preparations. The same has been true for HPLC in

recent decades& mostly used in analysis of Chinese medicine [78-91]. Reverse phase (RP) columnis also used in HPLC. Perhaps the most popular columns are used for the analytical separation of herbal preparations. It should be noted that the optimal separation conditions for HPLC include as many elements as others like mobile phase composition, pH adjustment, test design, pump pressure etc. Optimal allocation appears to be generally desirable [88, 91]. Some new techniques for better separation recently developed in the field of fluid research. These are micellar capillaries, Chromatography (MECC) [92], rapid reflux Chromatography (HSCCC), low pressure size exclusion Chromatography (SEC)[93], reverse phase ion pairHPLC (RP-IPC-HPLC)[94,95] and strong anion exchangeHPLC (SAX-HPLC)[96]. It provides new opportunities to correctly split some specific passages. Some herbal remedies. On the other hand, benefits HPLC is versatile for chemical analysis. Although it is a compound of herbal remedies, it is the most common. The detector used in HPLC refers to a short-wavelength UV detector; too many chemicals seem unable to do the job. Compounds in herbal preparations are not chromophores. Therefore, usage has increased greatly HPLC analysis coupled to evaporative light scattering detection (ELSD) in the last decade. ELSD is an excellent detection method for analysis of necromogenous compounds [97-99]. Many direct HPLC analysis are available for pharmacologically active ingredients of herbal preparations. ELSD responses are characterized by size, shape, and number of eluate particles rather than analytical structures and/or chromophores such as UV detectors. This method is especially suitable for Chinese medicine fingerprinting. At the same time, it can also be used for qualitative analysis or structural elucidation of chemicals. The HM component is not possible by simple HPLC. So, hyphenated methods are used. HPLC such as analytical HPLC-MS and HPLC-NMR techniques are used for medicinal herbs.

Electrophoretic method

Capillary electrophoresis was introduced in the early 1980s. As powerful analytical and separation method[85] andsince then, it has grown almost explosively. This allows for an efficient way to document sample purity/complexity.It can handle all types of charged sample components, from simple inorganic ions to DNA. Hence, electrophoresis like capillary electrophoresis has grown a lot[86–108].The implementation was generally similar to that of liquid chromatography. Most of the methods used are capillary zone electrophoresis (CZE), Capillary gel electrophoresis (CGE) and capillary isoelectric focusing (cIEF). CE is promising for the separation and analysis of the active ingredients of herbal medicines. As only a small amount of medicine is needed samples can be analyzed quickly with very good resolution. It is also a good tool for chemical fingerprinting of herbal medicines. Recently, several studies have reported herbal remedies and two types of medicinal compounds, namely alkaloids [95–102] and flavonoids [103–108] which have been extensively studied. Overall, CE is a comprehensive and strong department. An instrument with high separation efficiency and

selectivity is used for analysis of mixtures of low molecular weight components as pointed out by Shibabi and Hinsdale [109]Rapid development of capillary electrophoresis increasing. The goal is to increase resolution and throughput rather than absolute repeatability and accuracy which is a successful way to improve fertility. Both mobility data and integrated data are based on internal data standard [110].CE only provides a limited picture of the actual functionality. In the field of fingerprints in Chinese medicine, heterogeneity and polydispersity of herbal preparations is possible. It limits simplistic inference and many artifacts. This may be caused by the chemistry of the separation buffer chosen. There are implicit instrumental constraints but we believe it approaches CE and capillary electro chromatography. It contributes to a better understanding of the solution. The action of herbs, especially when used additionally combined with power analysis (offline or online) sensor.

Hyphenation Process

Termination procedure or hyphenation process chromatography has been integrated in the last 20 years. On-line separation system with spectroscopic detector inside to obtain structural information for existing analytes is becoming the main approach for model target identification and confirmation of unknown compound. Many analytical (trace level) problems in herbal research have been addressed by column liquid chromatography or capillary combination, gas chromatography using UV-vis or mass spectrometry (HPLC-DAD, CE-DAD, GC-MS and LC-MS respectively). It becomes a suitable method for the analysis of spices approximate. It is also true that they are complementary. In some cases, the information is urgently needed. This can be ensured, for example, by atomic emission. Fourier transforms infrared (FTIR), fluorescence emission (FE) or nuclear magnetic resonance (NMR) spectroscopy. From a practical point of view, you can get good results because you need more& more information to manage the most complex analysis systems such as plant medicine models. Hyphenated tool data is also called double-sided data, i.e., a string. It could be another way for chromatograms and spectra. It provides much more information than a single traditional meaning chromatograph. In the late 1970s we will have more opportunities dealing with difficult problems of herbal analysis and herbal quality control issues.

GC-MS and Herbal Medicines

GC-MS is a sensitive and selective method that can provide information on molecular analysis methods; molecular weight and structure of molecules. Combining chromatography and mass spectrometry offers the advantages of chromatography, separation method and mass spectrometry as an identification method. There are many ionization methods for mass spectrometry. It separates compounds and then dissociates ions. General way ionization used with gas chromatography Electron Impact (EI) and Electron Capture Ionization (ECI). EI is mainly configured to select cations. ECI, on the other hand, is usually configured for negative ions (ECNI). EI is

particularly useful for routine analysis and recommendations as well as repeated mass spectra with structural information. GC-MS was the first to succeed an on-line combination of chromatography, mass spectrometry. So is widely used for essential oil analysis of crude drugs.[100-124].The most qualitative and relatively quantitative composition [115-119,125,126] is used for the analysis of medicinal plants. The drug has at least two important advantages. GC-MS, namely: (1) capillary column GC-MS: In general, very good separation ability, can produce high quality chemical fingerprint; (2) combined with mass spectrometry and corresponding mass spectra databases can provide information on the qualitative and relative quantitative composition by GC-MS, which will be very useful in the future as well as in research to determine relationships between chemicals. The composition and pharmacology of the plant are under further investigation. Therefore, in our opinion, GC-MS is the best tool for volatile chemical analysis of compounds in herbal preparations and peak detection.

Conclusion

Quality control of medicinal plants aims to ensure quality, safety and efficacy. This study presents multiple chromatographic fingerprints as a quality control strategy for a complex herbal formulation consisting of multiple chromatographic fingerprints and providing a complete chemical characterization of the analytes & drugs instead of a reported chromatographic fingerprint. Western and traditional Chinese medical practices represent totally different philosophies. This is not a simple exercise of applying modern technologies to quality control of the products that have been in constant use for centuries. The progress on quality control of herbal medicines discussed in this review is just at its beginning stage of a long journey. The proposal of the use of chromatographic fingerprints of herbal medicines for quality control of herbal medicines is definitely a progress. However, using the chemical fingerprints for the purpose of quality control of herbal medicines can only address to the problem of comparing the integrated sameness, difference and controlling their stability of the available herbal products. The complex relationship between the chromatographic fingerprints and efficacy of the herbal medicines (QRFE) is not taken into account yet, which seems to be the most important aspect for the quality control of herbal medicines. As it is well-known that the efficacy of traditional herbal medicines has a characteristic of a complex mixture of chemical compounds present in the herbs, thus how to evaluate reasonably their relationship is obviously not a trivial task. THMs represent a much more daunting challenge due to the natural variability of the individual herbs and the chemical complexity of the formulations. Moreover, the chemical profile by itself is insufficient in determining the efficacy of TCM. This is where biochemistry, molecular biology, and cell biology are invaluable in establishing quantifiable and reproducible assays. Chemical fingerprints might be linked to these biological assays to provide assurance of efficacy and consistency. But the research work on this aspect,

to our best knowledge, is far from sufficient to meet the criteria needed. Thus, the researches concerning the relationship between the chromatographic fingerprints and efficacy of the herbal medicines are urgent requirements for the quality control of herbal medicines. On the other hand, the works on possible contaminations in herbal products, such as excessive or banned pesticides, microbial contaminants, heavy metals, chemical toxins, should be also conducted concurrently. In fact, the research field of quality control of herbal medicines is really interdisciplinary research. It needs crossover of chemistry, pharmacology, medicine and even statistics to provide a platform for the quality control of traditional herbal medicines and further to discover the novel therapeutics composed of multiple chemical compounds.

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