Review Article

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INNOVATIONS AND ADVANCEMENTS IN HERBAL DRUG STANDARDIZATION: A REVIEW

Saleemulla Khan¹ and Aswatha Ram HN^{2*}

¹Assistant Professor Selection Grade, Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India

²Associate Professor, Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India

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*Corresponding author

E-mail: aswatharam@gmail.com

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ABSTRACT

WHO has been publishing guidelines for assessment of quality of herbal raw material from time to time, however now it is emphasizing on standardization of herbal preparations. As there are different kinds of preparations available in the traditional systems, a common technique of standardization is not available. This article reviews the recent techniques that are used in herbal drug standardization so as to find a feasible and affordable method of standardization.

Keywords: Capillary electrophoresis, Chemometrics, Combinatorial markers, Comprehensive dissolution, SCAR markers

INTRODUCTION

Since the dawn of civilization, herbs and herbo-mineral drugs have been used to treat human diseases. Herbal medicines are getting popular due to the belief that, these are cheaper and locally available remedies with fewer side effects. However, lack of standardization techniques and non-availability of marker compound or such traditional medicines is the only drawback of these medicines. Standardization is necessary to ensure the quality, safety and efficacy of the herbal preparations. During the past decades, efforts have been made to develop suitable standardization techniques for these herbal drugs.

Generally one or more herbs are used in herbal preparations which are considered as herbal finished herbal products. These herbal drugs may contain excipients in addition to the active ingredients. However, herbal finished products or mixed herbal product to which synthetic or chemically defined compounds or isolated constituents from herbs have been added, are not considered as herbal drugs⁸.

Standardization of herbal drug(s) means adjustment of a herbal preparation to a defined quantity of its constituents with a known therapeutic effect¹. Standardization ensures quality, quantity and therapeutic efficacy of each dose of ingredients in a predefined manner². Good Manufacturing Practices (GMP) implementation is another requirement for the standardization of herbal formulations³⁻⁵. Such abundance of regulations avoid batch to batch variations and minimize errors and increases the acceptance of polyherbal formulations⁶. The therapeutic efficacy in herbal medicines is generally attributed to the synergistic effect of the biologically active constituents which needs to be standardized⁷.

The traditional Ayurvedic medicine employs over 1200 different herbs and about 65% of the Indian population use herbal medicine on a regular basis. Herbal medicines are popular even in the developed countries. The Canadians (50%) and French (75%) have tried complementary or alternative medicine (herbal

remedies) for certain ailments, according to WHO. A traditional herbal medicine, Kampo is prescribed by about 85% of medical doctors in Japan together with modern medicine. The thorny issue is standardization of herbal medicines, as they contain hundreds of chemical constituents with or without therapeutic effects may be with a little or no evidence⁹. Therefore this article reviews recent techniques in standardization of herbal products; a basic scheme¹⁰ of herbal drug standardization is shown in the Figure 1.

Chemometrics

In the year 1971 a Swedish scientist Svante Wold coined the term "kemometri" in Swedish which is termed as "Chemometrics" in English¹¹. The most commonly used methods in standardization of herbal medicines are chromatography. Though the techniques are powerful, they suffer with major drawback such as improper identification of the separated compounds. Hyphenated techniques in addition to chromatography such as LC-MS, LC-MS-MS, has paved way for better identification and clear understanding of the phyto-mixtures. Chemometrics further analyzes the spectroscopic data and helps in affording better chemical information. Chemometric resolution method and principal component analysis (PCA) is the commonly used technique and the scheme of instrumental data interpretation by chemometrics is presented in Figure 2¹².

Capillary Electrophoresis

Because of the versatility and high separation power, Capillary electrophoresis (CE) meets the criteria for quality control of herbal drugs. A wide range of polarity and molecular weight compounds can be analysed¹³⁻¹⁴. In Capillary zone electrophoresis (CZE), separation is based on the charge to mass ratio of the analytes. Plant secondary metabolites such as Alkaloids, Phenolic acids and Flavonoids are analysed easily by CZE. Optimization of CZE methods specifically for the analysis of phytochemical compounds has been reviewed by Li *et al*¹⁵.

Plant extracts containing alkaloids can be protonated easily and form water-soluble salts and the aqueous acidic electrolytes are often used as background electrolyte for CZE analysis. Hydrophobic compounds get more solubilized in non-aqueous solvents and further improve selectivity as organic solvents are widely used in CE. Aconite roots electropherogram¹⁶ is depicted in Figure 3.

Mono and polysaccharides in herbal drugs (Moutan Cortex) was standardized by applying CE. Copper working electrode was applied at a constant potential in a strong alkaline media for the analysis of carbohydrates. *Paeonia suffruticosa* was identified in Moutan Cortex using the markers such as paeoniflorin and paeonoside and other sugars¹⁷.

Dissolution Test (Comprehensive)

Release of active principles from the solid dosage forms is the crucial step for bioavailability and efficacy. For the quality control of oral dosage forms, active pharmaceutical ingredients are identified by dissolution studies. Dissolution study for herbal medicines is difficult due to complex nature of active principles¹⁸. In herbal medicines dissolution is limited extremely because of the poor understanding of the lead molecules characterization and their bioactivity. Moreover, factors such as origin, harvesting time and method of extraction of the herbal raw material, govern the specific formulation chemical composition to a considerable extent¹⁹⁻²⁰.

Biological fate of some herbal constituents could be attributed to the bacterial biotransformation²¹, but still dissolution is the prerequisite for permeation to the bio membrane. Herbal solid dosage forms need to be tested for *in vitro* dissolution to consider the bioavailability. Previous to principal component analysis (PCA), Pareto scaling highlighted the quantitative performance by loading of peaks selectively which indicates drug release and dissolution rate of clinically implicated molecule.

For the first time, a method was developed and validated for the comprehensive dissolution test for *Ginkgo biloba* tablets by integration of profiling of chemical and strategy of self-reference (peak by peak). Self-reference samples chromatographic fingerprints due to the translation by PCA into chemical profiles which is the normal gross concentrations. This method was used to detect the simultaneous release of the detected constituents after the development of a HPLC fingerprint with the help of a principal component analysis and the fingerprints of *Ginkgo biloba*²² is represented in Figure 4.

Scar Markers

Randomly Amplified Polymeric DNA (RAPD) has been used in the identification and characterization of proteins in different biological systems. However, the techniques lack reproducibility which is a major drawback. Therefore, the technique cannot be used for the herbal drugs authentication. Other PCR and non-PCR based markers like AFLP, ISSR, SSR and RFLP have also been used for the authentication of herbal drugs. Unfortunately even these markers suffer with disadvantages like high cost, radioactive isotope use, and sequence information requirement etc.

The reproducibility of RAPD has been improved by the conversion of amplicons of RAPD into Sequence Characterized Amplified Region (SCAR) markers to make it reproducible as compared to RAPD markers alone. The method has been validated for reproducibility and hence can be safely used for

the authentication of medicinal plant materials used in the preparation of traditional medicines²³.

Combinatorial Markers

Selection of marker compounds may be sometimes irrelevant to the bioactivity in many cases. Therefore, Zi-Qi Shi *et al*²⁴ proposed a universal strategy for the identification of combinatorial markers. These are bioactive and considered as chemical markers for standardization. Some common components in different batches of medicines were identified for fingerprinting and quantification. *Lycoridis radiatae* bulbs were used as an example and ungerimine and galanthamine were chosen as effective combinatorial markers which the authors found by fingerprint-bioactivity modeling (bioactivity and quantification of compounds) and Acetylcholinesterase inhibitory activity. This method was applied to the unknown samples also and regarded as useful for the discovery of effective combinatorial markers (ECMs) of new herbal drug candidates. The strategy²⁴ for standardization is depicted in Figure 5.

Marker Compounds

There are three types of marker compounds²⁵ viz., bioactive markers [e.g., vasicine, curcumin, piperine (responsible for the activity which is claimed for a particular drug)]; chemical markers [e.g., quercetin, lapachol, rutin (constituents neither specific to the drug nor to the activity of the herbal drug)], and general markers [e.g., gallic acid, lupeol (compounds distribution is wide in plants)].

Marker Based Standardization

SJT-DI-02 (marker based standardized) is a patented, novel and efficacious polyherbal formulation used for the treatment of diabetes. The formulation consists of dried extracts of *Acorus calamus* (rhizomes), *Aegle marmelose* (leaves), *Benincasa hispida* (fruits), *Chlorophytum arendinaceum* (roots), *Eugenia jambolana* (seeds), *Ocimum sanctum* (leaves), *Punica granatum* (pericarp), *Tamarindus indica* (seeds). Different fractions of extracts were mixed to prepare the formulation. The polyherbal formulation was standardized by using four different markers (marmelosin, gallic acid, lupeol and asarones). TLC system was well developed first followed by HPTLC. Quantification of marker compounds was done by TLC densitometric method. Overlay of absorption spectra was used to know the purity of bands due to the marker compounds in the extracts, and confirmed. The developed HPTLC method was found to be sensitive, reproducible and rapid²⁶.

Simultaneous determination of seven bioactive compounds such as ephedrine, amygdalin, liquiritin, benzoic acid, isoliquiritin, formononetin and glycyrrhizic acid was carried out in San-ao decoction (a traditional Chinese prescription) and its various combinations using HPLC. A validated method was adopted for the analysis briefly detection was carried out by diode array (DAD) at 210, 254 and 360 nm; XTerra C(18) column as stationary phase and acetonitrile and a buffer solution ((0.02 mol/L potassium dihydrogen phosphate and adjusted to pH 3 using phosphoric acid) as the mobile phase. The flow rate was 1.0 mL/min. A wide variation was observed in the contents of the compounds and useful in illustrating the possible drug interactions after the combination of some herbs in the different formulations²⁷.

A high performance liquid chromatography (HPLC) method was developed and validated (ICH guidelines) for the analysis of

ferulic acid in Asafoetida and one poly-herbal formulation. HiQSil ODS C-18 was used as the column and the mobile phase was acetonitrile: 10% acetic acid (20:80 v/v). The method can be used for estimation of ferulic acid in formulations containing Asafoetida²⁸.

Reverse phase high performance liquid chromatography (RP-HPLC) method was developed for the estimation of trigonelline from *Trigonella foenum-graecum* and its marketed herbal formulations such as Dibet powder and Amyron syrup. Cosmosil CN-MS was used as the column and eluted with solvent system, methanol:distilled water [95:5, v/v; pH 3.5 using hydrochloric acid]. Photo Diode Array detector at 267nm was used for the detection²⁹.

Rapid RP-HPLC analysis of glabridin from the crude drug and herbal formulations was developed and validated. C18 column was used and the mobile phase was water and acetonitrile in a gradient elution manner with a flow rate of 1 mL/min. 14.9 ± 0.02 min was the Retention time. This method can be used for the analysis of glabridin in herbal formulations containing Licorice as one of the ingredients³⁰.

Nardostachys jatamansi DC is used as herbal medicine singly and in multi-herbal formulations UPLC-QTOF MS, a validated method was developed for the identification of nardin in *N. jatamansi* samples. Acquity BEH C(18) column was used with a gradient elution of methanol-water and 3 mm ammonium acetate. Negative ionization mode of QTOF mass detector was used. Authentication and quantification of the marker was done in 4 minutes using the chromatography³¹.

Embelin (marker) based standardization was developed and validated in plant *Embelia ribes* and its polyherbal formulations. Embelin was quantified by Reversed-phase high-performance liquid chromatography and coupled with diode array detection (RP-HPLC-DAD) and the method was validated. Selected phytopharmaceuticals were demonstrated using this method which can be recommended for marker based standardization and quality control of *E. ribes* containing formulations³².

Sesamum indicum seeds and its oil had been used in Ayurveda since antiquity. Lignans which are main and biologically active compounds in sesamum oil were identified as the marker compounds. A validated HPTLC method has been developed and validated for the quantification of sesamin and sesamol (lignans) of Sesamum oil and its polyherbal formulations including the commercial ones. Densitogram followed by charring of the plate was also developed for marker based standardization of formulations containing Sesamum oil³³.

A validated HPTLC method of analysis for Sennoside A and Sennoside B was developed for its quantitative analysis. Silica gel 60 GF₂₅₄ HPTLC plates were used in the methanolic extract analysis. The spots were visualized under UV and scanned at 350 nm for absorption/reflection mode. Linearity in the range of 200-1,000 ng was observed in the calibration curves. 0.991 for sennoside A and 0.997 for sennoside B were the correlation coefficient. The percentage recovery was 95 and 97% respectively for Sennoside A and Sennoside B and hence a

reliable and reproducible method. LOD and LOQ were found to be 0.05 and 0.25 µg/g respectively. They found that lot of variation in the content of Sennosides was observed from the Indian marketed poly-herbal formulations containing Senna³⁴.

Ayurvedic Formulations

In Ayurveda, compound formulations prepared from the plants are extensively used. Plant is a mixture of compounds and desired activity may not be exhibited by one compound. Some compounds may be synergic in action or some may neutralize the possible side effects by counteracting. Therefore, it is desirable to use many plants with common anticipated activity so that the final formulation will show maximum activity in a concentrated manner³⁵.

Ajmodadichurna is a polyherbal Ayurvedic medicine used as carminative and antispasmodic. The churna was prepared, standardized and compared with a marketed sample. Standardization was based on organoleptic characters, physical parameters and physico-chemical characteristics³⁶.

Bhasmas (Medicated Ashes) are prepared by incineration of purified herbal extracts or minerals. Bhasmas are considered to be safe for 2 reasons; one, these formulations are not metabolized in the body and second, they maintain high alkalinity which neutralizes harmful acids. These preparations are formulated using grasayoga, sindora, parpati, etc. However if iron, copper and sulphur are used; then the role of its component in the final products must be specified. Bhasmas being tiny particulate preparations particles measuring in nano meters, absorption and assimilation of the preparation in the body is facilitated. Therefore, bhasmas can be termed as ancient nanomedicine³⁷.

A comparative standardization of Trivanga bhasma was carried out for In-house prepared bhasma with a marketed preparation. Evaluation was done for physical properties and chemical standardization. Fourier transform infrared spectroscopy (FTIR), Atomic absorption spectroscopy (AAS), Scanning electron microscope (SEM), X-ray Diffraction (XRD), Thermogravimetric analysis (TGA) and Atomic force microscopy (AFM) were applied for standardization. The samples were also subjected to toxicological screening and antidiabetic including diuretic activity studies. Fingerprinting of Trivanga bhasma was reported for the first time using an analytical technique³⁸.

Brahmivati (Tablet) contains thirty eight ingredients and is used in the treatment of epilepsy and mental disorders. HPLC-UV method was developed and validated for the analysis of Bacoside A3 and Piperine which are used as the reference compounds of *B. monnieri* L. and *P. longum* L. respectively. Results showed variation in the content in marketed samples when compared with the In-house sample analysis³⁹.

Thus, a plethora of scientific methods are available for the standardization of Ayurvedic products as of now, however Kurele⁴⁰ opines that it is not the products alone but even the premises of ASU products must be standardized as per the regulations.

Figure 1: Herbal drug standardization scheme (Courtesy¹⁰)

Figure 2: Scheme of interpretation of complicated data from Instruments by chemometrics. (Courtesy¹²)

Figure 3: Typical electropherogram of Aconite roots. (Courtesy¹⁶)

Figure 4: HPLC fingerprints of *Ginkgo biloba* tablets in the analytical dissolution test. (Courtesy²²)

Figure 5: Standardization strategy for characterization of ECM as active markers. (Courtesy²⁴)

[HM-Herbal medicines, QTOF-MS (Quadrupole-time-of-flight–Mass spectroscopy), MLR and BP-ANN are the two Chemometric methods, ECMs-Effective combinatorial markers]

CONCLUSION

Although information on standardization of herbal/ traditional medicines is plenty, yet there is a long way to go. One of the most commonly encountered problems is non-availability of marker compounds. Further, poor understanding of therapeutic activity and synergism offered by a mixture of constituents is a major hurdle in the standardization of herbal products. Efforts are being made to establish the newer and better techniques for standardization of herbal products. Application of chemometrics, capillary electrophoresis and combinatorial markers, has added new dimension to existing knowledge. This review also focuses on comprehensive dissolution techniques for herbal formulations.

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