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Invited article

Standardization of Medicinal Plants for the Sustainable Exploitation of Biodiversity

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Abstract

A supply of consistent raw plant material provides the basis on which manufacturing controls act to yield reproducible herbal medicinal products. Therefore, it is important to enact standards and specifications in herbal monographs that cover botanical, chemical, pharmacognostic, and physical properties to authenticate and standardize medicinal plants to assure consistency of the raw material. An important part of this effort is to develop analytical methods for the qualitative and quantitative assessment of raw plant materials using appropriate chromatographic methods. For example, a chromatographic assay, such as liquid or gas chromatography, could be included in a monograph to determine the constituent(s) with known therapeutic activity or an active marker or multiple analytical markers. The harmonization of standards in different regions and countries is intended to coordinate the quality assessment and facilitate access to international markets for these products. Standards defined by regional herbal monographs and quality requirements enacted by a harmonized multinational regulatory environment would be in the best interest for the sustainable development of herbal and traditional medicines.

Keywords: Medicinal plants, Standardization, Herbal monographs, Sustainable exploitation, Biodiversity

Introduction

Herbal medicinal products (HMPs) occupy a significant place in consumer consciousness worldwide and are an important part of healthcare in most developing countries. There is a growing interest in the integration and use of herbal and traditional medicines. Such integration often includes herbal medicines as a therapeutic option in addition to allopathic medicine. Global interest from the medical and scientific communities has given herbal medicinal products a place in evidence-based medicine. The Consolidated Standards of Reporting Trials (CONSORT) statement was developed to improve and clarify the necessary information that should be reported for controlled clinical trials[1], and these standards are supported by regulatory authorities. However, there are major barriers preventing scientists, the medical establishment, and policymakers from accepting HMPs as substances equivalent to 'orthodox' medicines, both in the developed and developing world. Many of the concerns that need to be addressed are related to quality, safety, and efficacy[2].

The goals of the 2014–2023 World Health Organization (WHO) Traditional Medicine Strategy[3] are to support Member States in (1) harnessing the potential contribution of traditional and complementary medicine (T&CM) to health, wellness, people-centered healthcare, and universal health coverage (UHC), and (2) promoting the safe and effective use of T&CM through the regulation, research, and integration of T&CM products, practices, and practitioners into the health system, as appropriate. The research community has a pivotal role to play in advancing this global agenda. Although 75 Member States had established national research institutes for T&CM as of 2018, many governments lack the technical expertise or resources to adequately document the national T&CM landscape, including an assessment of the related need, demand, and resources. This documentation begins with assessing the use patterns among specific population groups, the level of self-medication with traditional agents and practices, and quality assurance practices, among other areas of basic inquiry. Fostering in-country and international collaborations among researchers and governments is critical. The WHO Traditional Medicine Strategy 2014–2023 offers concrete suggestions to move forward. There is an increasing awareness and general acceptability of using herbal drugs in today's medical practice. The increased use of herbal products has also given rise to various forms of abuse and adulteration of these products, leading to consumer and manufacturer disappointment, and in some instances fatal consequences. These challenges are difficult to address, making the global herbal market unsafe. This review seeks to educate herbal medicine stakeholders on the need for establishing quality parameters for the collection, handling, processing, and production of herbal medicines and to advocate for the application of such parameters to ensure the safety of the global herbal market. The processes of good quality assurance and the standardization of herbal medicines and products are also discussed[4-12].

Quality for safety and efficacy

The quality, safety, and efficacy of herbal drugs must be ensured to provide a sound scientific footing for the use of herbal products, thereby enhancing consumer confidence and improving business prospects for herbal medicines worldwide[2,13]. The single and most important factor that stands in the way of a wider acceptance of herbal drugs is the non-availability or inadequacy of standards for verifying and ensuring their quality. Quality encompasses statutory requirements, technical expertise, and market expectations. Statutory requirements guarantee a set of minimum standards, the violation of which leads to punishment; these are imposed by authorities and are necessary to do business. Pharmaceutical companies face great challenges when trying to gain access to different herbal medicine markets because they often must comply with legislation from multiple countries, with diverse requirements and standards. International communication within the scientific and regulatory community is necessary to develop an appropriate regulatory environment for HMPs.

Technical experience and quality assurance measures help to ensure quality throughout the standardization, production, testing, and monitoring processes[4,5,13]. Market expectations are also very important and can determine the fate of the product, and both the product and the packaging standards play an important role. Quality can be achieved by following professional guidance, conducting regular monitoring, maintaining proper records, taking appropriate corrective measures when necessary, and culturing the right attitude. Safety is a fundamental principle of herbal medicines in healthcare and is a critical component of quality

management. It is a misconception that all natural products are safe, as there is the possibility of innate toxicity, poor product quality, mistaken use of the wrong species, and adulteration with other components or even with potent chemical substances. Incorrect dosing, interactions with other medicines, or the misuse of herbal drugs by healthcare providers and consumers could occur.

The simultaneous use of herbal drugs with allopathic drugs might lead to adverse interactions. For example, Ginkgo biloba L. adversely interacts with warfarin, aspirin, ticlopidine, dipyridamole, and clopidogrel; Hypericum perforatum L. interacts with anti-depressants and warfarin; and Ephedra gerardiana Wall. ex Stapf interacts with decongestants, stimulants, and caffeine. 14-15 The detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems when using an herbal drug needs to be monitored by pharmacovigilance to strengthen the credibility of herbal drugs[2,16].

Raw materials

The majority of the medicinal and aromatic plants used by the herbal drug industry come from wild collection, comprising greater than 80% of the medicinal plants in trade. Added to the overdependence on wild plants is the over-exploitation of these bio-resources due to destructive, indiscriminate, and inappropriate methods of harvesting, which has led to the extinction of many species. Because there is little understanding of the amounts and types of available medicinal plants, the industry using these raw materials from wild sources cannot assess how much damage is being or whether the harvesting is sustainable[12].

Barely 10% of the raw material comes from cultivated sources, which would offer buyers a more consistent quality and a lower risk of adulteration compared with the collection of wild counterparts. Modern pharmaceutical companies entering into the herbal drug business prefer to use standardized extracts as the active botanical ingredient for herbal drug formulations. Again, there is no control over the quality of these extracts, and the industry produces its own specifications for these standardized extracts.

The standardization of herbal drugs and preparations thereof is not only an analytical operation—it does not end with the identification and assay of an active compound. Standardization should encompass the total information and quality controls that are necessary to guarantee the consistency of the composition.

Major causes of inconsistency

Regional linguistic nomenclature for plant collectors creates confusion in the exact botanical identity of plant materials. There could be ecotypic (Eclipta prostrate (L.) L., genotypic (Acorus calamus L.), or chemotypic (Withania somnifera (L.) Dunal) variability. The harvesting time period and plant growth stage influence the quality of the raw material. Post-harvesting practices such as the drying and garbling methods and the packing and storage conditions also influence the quality of the raw material. Good gathering practices (GGPs), good agricultural practices (GAPs), good harvesting practices (GHPs), and good herbal processing practices (GHPPs) can reduce the levels of inconsistencies in the quality of the raw material. GHPP guidelines are intended to supplement technical guidance for processing in the post-harvest stages[17].

Standardization of raw plant materials[4-12]

Identification:

Pharmacognostic identification is a sine qua non for botanicals and calls for well-trained analysts in histology and taxonomy. Morphological, histological, and taxonomical

identification were previously considered sufficient to positively identify a botanical. However, with the advances in analytical technology over the last four decades and the availability of several spectrophotometric and chromatographic techniques that provide detailed and thorough information, a more accurate identification can be achieved. Among the various chromatographic techniques, thin-layer chromatography (TLC) is a good choice because it is inexpensive, provides a wealth of information on the nature and possible number of compounds present in the herbal raw material, and is readily available in laboratories worldwide[5-6,8].

In the chemical identification of a raw material, a marker substance characteristic to that particular botanical is assayed and quantified[18-19]. Because chromatographic conditions may vary, this can be achieved by comparing the results to an authentic reference standard of the marker substance. Other chromatographic techniques such as gas chromatography (GC) and high-pressure liquid chromatography (HPLC) are powerful tools and could also be easily employed in the identification of botanical raw materials.

Limits for impurities[7-11]:

A test requirement for foreign organic matter would ensure a low amount of contamination with extraneous matter, such as dirt and other plant parts that are not covered by the definition of the herbal drug. Because sand and soil are predictable contaminants of botanicals, test requirements for total ash, water-soluble ash, acid-insoluble ash, residue on ignition, and sulfated ash would be expected to limit such contaminants.

Test requirements for heavy metals in botanical raw materials are probably more relevant for the parts of plants growing under the ground than for the aerial plant parts. However, to ensure that processing operations such as grinding or milling of the material do not lead to contamination, testing for heavy metals should be conducted.

Microbial limits[7-11]:

If the plant material reaches the consumer without any reduction in bioburden, limitations on microbial contamination are in order unless the material is expected to be boiled in water prior to consumption. A more permissive standard for microbial limits would be acceptable when the bioburden of the material reaching the consumer has been reduced via subjection to extensive processing, such as boiling with water or solvent extraction. Pathogens such as Salmonella should be absent, and there should be restrictive limits on Enterobacteriaceae and E. coli in any material that will be taken internally. A lower level of yeasts and molds and a limit on total aerobes are considered appropriate in plant materials for topical use. The presence of aflatoxins detected by chemical means is generally independent of the number of viable molds that are detected using microbiological methods. However, a screening test based on a serological response to Aspergillus antigen as a first test and (if positive) followed by an aflatoxin test would be appropriate. Differential limits would apply according to the intended use of the raw material and the final medicinal product. Some examples are provided in Table 1[20].

Pesticide limits[4,11]:

Maximum residue limits for pesticides in medicinal plants is one of the major issues in standardizing these products in view of the global and widespread use of pesticides for plant cultivation. This issue is challenging owing to the copious and uncontrolled use of a wide variety of organochlorine and organophosphorus pesticides.

Well-validated analytical methods for the quantitative determination of pesticides, such as gas chromatography coupled with

Table 1: Limits for microbial contamination in herbal materials

Microbe	Allowable limit in material for topical use per gram	Allowable limit in material for internal use per gram
Aerobic bacteria	10^7	10^5
Yeasts and molds	10^4	10^3
Escherichia coli	10^2	10
Other enterobacteria	10^4	10^3
Salmonella	absence	absence
Clostridia	absence	absence
Shigella	absence	absence

mass-spectrophotometry, are used in many laboratories; however, these methods must be carried out by specially trained technicians. Harmonized methods of analysis for pesticide determination as part of public standards are not difficult to achieve, although the pesticides to test for must be established. While industrialized countries have taken necessary actions to limit the number of pesticides that are allowed in plant cultivation, a different situation exists in developing nations. The complexity of the situation is compounded by the fact that the list of banned and permitted pesticides varies from country to country. In view of this, it is necessary for the label of the medicinal plant material to indicate the country of origin when entering international commerce, as dictated by the World Health Organization guidelines. This enables the importing country to test the imported plant material for those pesticides allowed for use in the country of origin. While this may sound straightforward, it requires the preparation of an enormous number of pesticide standards for quantitative determination. This perhaps has led the WHO to suggest testing for a minimum number of pesticides in medicinal plant material. The best solution for this problem, as WHO experts suggest, would be to develop and establish lists of pesticides that would be permitted worldwide for use in the cultivation of botanicals and those that are not desirable.

Chromatographic fingerprint profile[5-6, 10,12-13,18-21]:

Unlike synthetic organic medicinal compounds that exhibit a predictable pharmacological activity at a given dosage, the world of botanicals is quite different in the sense that it is not always known with certainty what constitutes the active ingredient(s). It is generally believed that the reported pharmacological action of a botanical is due to more than one constituent acting synergistically with other constituents that are present. From a pharmacopeial perspective, improved quality control of raw materials can be achieved by specifying a quantitative test procedure to determine the range or a minimum content of a marker substance or an “active” ingredient.

A chromatographic fingerprint profile represents the qualitative/quantitative determination of various components present in a complex plant extract irrespective of whether their exact identity is known. Because of the enormous progress made over the past four decades, the standardization of raw botanical materials with respect to an active ingredient or marker substance can be achieved. Advances in the separation sciences have given a clear advantage to the chromategraphic methods over conventional titrimetric and spectrophotometric methods. Thin-layer chromatography, the simplest and least expensive chromatographic method, provides

much information on the composition of medicinal plant drugs and their preparations. Thus, TLC is the technique of choice for the positive identification of raw materials. Because TLC has limited ability to provide quantitative analysis, liquid chromatography—which provides simultaneous separation and detection—is the technique of choice for the quantitative determination of active ingredients or marker substances. The HPLC technique combines selectivity and sensitivity, thus providing a more reliable assessment. An example of this technique can be found in the United States Pharmacopeia and the National Formulary (USP-NF) online monographs for "ginger" and "powder ginger" that were published in Pharmacopeial Forum (Volume No. 40(6))[22].

In recent years, liquid chromatography mass spectrometry (LC-MS) has been increasingly applied in the analysis of medicinal plant materials.21 LC-MS is an expensive technique, but the cost may be justified by the wealth of information it provides. The information generated by LC-MS can be used in the development of public standards for plant drugs. The method submitted to the USP utilized LC-MS to identify the peaks of various isomers of gingerols and shogaols, and their retention times are used in the liquid chromatography method for the quantitative determination of these compounds.

Pharmacopeial monographs[5-6,13]

The increasing number of herbal monographs that are being included in various pharmacopeias will help to advance the use of herbal medicines in the coming years. Herbal monographs are appearing in various pharmacopeias worldwide, e.g., the United States Pharmacopeia and the National Formulary (USP-NF), the European Pharmacopoeia, the American Herbal Pharmacopoeia (AHP), the British Herbal Pharmacopoeia (BHP), the Japanese standards for herbal medicines, the Pharmacopoeia of the People's Republic of China, the Ayurvedic Pharmacopoeia of India, and the Thai Herbal Pharmacopoeia. As yet, there are still no harmonized herbal monographs in the Association of Southeast Asian Nations (ASEAN). No pharmacopeia in the world is comprehensive enough to cover all medicinal herbs, and no pharmacopeia is able to give concrete methodologies for the routine quality control of medicinal herbs. This indicates the limitations of the basic approach of developing standards for medicinal plant materials that are in line with allopathic drugs.

The following criteria for prioritizing medicinal plants for ASEAN and regional pharmacopeial monographs may be adopted:

1) Some evidence of beneficial pharmacological action and a history of use in traditional medicine.
2) Absence of significant safety risks.
3) Interest of the regulatory agency.
4) Extent of use.
5) Inclusion of typical pharmacopeial monograph requirements such as:
   - definable plant species;
   - known characteristic chemical constituents;
   - availability of validated chromatographic or spectroscopic methods for the quantitative determination of characteristic chemical constituents;
   - availability of reference standard material for chemical identity and content assessment.

A more practical approach in the development and establishment of a pharmacopeial monograph is to specify a combination of spectrophotometric (UV, IR) and chromategraphic techniques (TLC, GC, HPLC) with the expectation that these would detect decomposition products that could arise owing to adverse storage conditions and the presence of foreign substances due to extraneous contamination.

Conclusion

Medicinal plant materials and preparations thereof have a definite role to play in healthcare systems around the globe. Standardization and quality control strategies that help to develop and establish the use of herbal drugs are in the best interest of every country. Communication and cooperation between regulators, the scientific community, and interested stakeholders in ASEAN and other countries will lead to the convergence of diverse regulatory environments. This will contribute to the worldwide availability of traditional medicines based on appropriate standards. To promote the use of quality herbal drugs in national healthcare systems, it is recommended that countries engage in the following efforts:

- Enact national policy and planning strategies for the development of medicinal plant-based drugs.
- Establish and implement regulatory mechanisms.
- Promote quality control procedures by setting standards for raw materials, production practices, and products.
- Promote the cultivation of medicinal plants adopting GAP and GHHP.
- Develop human resources.
- Mechanisms to allow regional cooperation within programs.
- Collation and exchange of information in regional databases of medicinal plants.
- Establish an herbal pharmacopeia for each region.

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