Challenges in standardization in Traditional Medicine / Herbal Drugs

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Abstract

The use of herbs and herbal extracts to treat diseases has stood the test of time. Herbal products/traditional medicine are composed of many constituents and are, therefore, capable of variation. The variability of the plant material is due to different conditions of growth, harvesting, drying, and storage. The polarity of the solvent, the mode of extraction, and the instability of constituents may also influence the composition and quality of the extracts. The quality criteria for herbal/traditional drugs are no doubt based on a clear scientific definition of the raw materials used. To prove the constant composition of herbal preparations, however, adequate analytical methods have to be applied. Depending upon whether the active principle of the plant is known or not, different concepts of standardization have to be applied in order to establish relevant criteria for uniformity. There are several challenges in doing this. The issue of marker content and standardization claims has unquestionably been the central (almost exclusive) focus of recent discussions on product quality. Traditional medicine / Herbal drugs can also be a looked at from the point of view of lead and drug development. Effective plant based drug discovery, however, requires an interdisciplinary approach wherein the pharmacognosist, chemist and the biologist work together.

Introduction

In recent years there has been a tremendous demand for herbal drugs especially in developed countries and this demand is increasing everyday in the world market. It is well known that traditional herbal medicines existed before the application of the modern scientific methods to health care **(**Subramoniam, 2001**).** Herbal medicines stood the test of time for their cultural acceptability and lesser side effects. The chemical constituents present in them are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body. Herbal/traditional medicines are made from renewable resources of raw materials by eco friendly processes and are expected to bring economic prosperity to the masses, growing these raw materials (Kamboj, 2000). In olden times, *vaidyas* used to treat patients on individual basis, and prepare drug according to the requirements of the patient. Today herbal medicines, however, are manufactured on a large scale in mechanical units, where manufacturers come across many problems such as non availability of good quality raw materials, and proper methodology for standardization, etc., (Harish Padh,2001**).** Exploring herbal/ traditional medicines in the context of modern science is the need of the hour for their optimum and proper utilization. Reproducible efficacy and safety of herbal products is based on reproducible quality. If herbal products are to be regarded as rational drugs, they have to be standardized and their pharmaceutical quality must be approved (Bauer et al., 1994).Also, their composition needs to be well documented in order to obtain reproducible results in pharmacological, toxicological and clinical studies (Bauer and Tittel, 1996).

WHO Guidelines for Quality control methods

The World Health organization has emphasized the need to ensure the quality of medicinal plant products by using modern quality control techniques and applying suitable standards. A series of tests for assessing the quality of medicinal plant products have been described. The tests are designed primarily for use in quality control laboratories in developing countries, and complement those described in the international pharmacopoeia, which provide quality specifications only for a few plant materials that are included in the WHO Model List of Essential Drugs. The test methods described here are the best methods currently available. In addition to these test methods, some suggestions regarding general limits for contaminants are included.

The need for standardization of herbal/traditional medicine

The primary reason standardization of herbal extracts is to achieve as much control in double blind clinical studies as is possible. According to the herbalist, Bob Brucea, standardization does have advantages. It produces a consistently strong product with guaranteed constituents. When you consider the quality of most commercial herbs, standardization at least assures, that they have something in it and that the correct herb is being used. Many herbalists look at the brighter side of the standardized herbal products as a quantum acceptance by more people including doctors and pharmacists who are accustomed to consistency and percentages of active constituents

Dr. Rudolf Bauer, one of the leading botanical research scientists in Germany states that if phytopharmaceuticals want to be regarded as rational drugs, they need to be standardized and pharmaceutical quality must be approved (Bone, 2000). Most consumers and even many manufacturers think of standardization as a fairly recent phenomenon, brought about by applying modern “state of the art” scientific methods to the production of herbal products. They would undoubtedly be quite surprised to learn that the call for standardized products has been a rallying cry in the industry for at least three hundred years (Cowen, 2001). Even today, some manufacturers use the term in its

historical context to mean an herbal extract produced to a consistent standard such as a specific extraction ratio, master formula or standard operating procedure. For the most part though, marketers have largely been successful in convincing consumers and the media that standardization means the product contains a specified amount of "active ingredient."

Challenges in standardization and designating markers

In the guidance documents published recently by the American Herbal Products Association (AHPA) (Eisner, 2001). "Standardization refers to the whole body of information and controls necessary to produce material of reasonable consistency. This is achieved through minimizing the inherent variation of natural product composition through quality assurance practices applied to medicinal plant growing, extraction and formulation development. Standardization can serve a number of purposes, including batch-to-batch consistency, confirmation of the correct amount of extract per dosage unit and positive control to indicate possible loss or degradation during manufacturing. While ensuring consistent marker content is an important aspect of standardization, it does not in itself equate to a standardized product. Standardization requires careful control of both raw material quality and manufacturing processes (Eisner, 2001).Standardization comprises of all measures leading to a reproducible product, without the addition of foreign substances (excipients, isolated active principles, etc.)

What is increasingly done now is to fixate on one plant component or similar components identifiable by assay and to standardize extracts to their content. Some believe that this quantitative measure will ensure qualitative results (i.e., an efficacious product). Others interpret this in a negative sense to mean that the product is an artificially manipulated extract in which:

- one or more compounds have been isolated and/or concentrated at the expense of all other constituents, or
- the extract is spiked with pure chemicals to achieve the claimed marker content, or

- fractionation and isolation procedures result in a substance that is no longer natural and is better defined as a pharmaceutical drug.

At the heart of the controversy surrounding standardization appears to be a great deal of confusion and misunderstanding as to what the purpose of standardization is and what the process actually involves. By nature, botanicals may be highly variable in their chemical makeup. The variability in the flavour, aroma and physical characteristics of wine and coffee from year to year and region to region provides a good analogy. There are numerous factors that may affect the ultimate chemical profile of a herb and the content of a specific marker, including intrinsic factors such as genetics and extrinsic factors such as growing, harvesting, drying and storage conditions. For example, a common garden breeding study of several St. John's wort accessions found that there was significant variation, not only in marker content throughout the growing seasons, but also between the same accessions grown at different sites, as well as between different accessions grown at the same site. This natural variation in the chemical make-up of herbs presents a considerable challenge, especially for researchers who must use products that are consistent in strength in order to obtain reproducible results. With the current technology, it is not possible to quantify the hundreds of chemical constituents present in herbal material in a timely and cost efficient manner. The compromise solution to this dilemma is to select a marker compound(s) and then ensure that every batch contains the same amount of that marker compound(s). This approach to ensuring consistency is based upon the assumption that the content of other constituents will vary in proportion to the marker compound; that if each batch contains the same standardized amount of marker, the content of other constituents will also be relatively consistent.

In Germany, where this practice originated, standardization to a specific content of active or analytical marker is only one of several means of maintaining product quality. The process of standardization was originally introduced to produce more consistent botanical products. Strictly speaking, a standardized product is produced by mixing batches of raw material to achieve the target marker content (Bussey, 2000). In practice, however, most manufacturers use normalization to achieve the target marker content. In normalization,

the concentration of product is adjusted by adding excipients or changing the extraction ratio.

In many cases, manufacturers are only concerned with ensuring that the minimum amount of marker specified on the label is present; the products may contain any amount of marker greater than the label claim. This defeats the purpose of standardization: to produce products that are consistent in strength. In other cases, the manufacturer's claim of standardization is based upon the fact that a standard formula or extraction technique is used. As one expert recently remarked, "there are no standards in standardization," (Leung, 2001) and a standardization claim does not necessarily mean consistent product quality.

The market's emphasis on marker content and standardization has been a boon for unethical businessmen. It is much easier to pass off adulterated materials to companies that only assess marker content. The ambiguity of the term 'standardization' facilitates questionable, if not outright fraudulent practices. For example, the strength of an extract is expressed as the extraction ratio: a 10:1 extract means that 10 kilograms of the plant material were extracted to yield a total of 1 kilogram of native extract or 10 percent extractives. If only 1 kilogram of extract is obtained from 100 kilograms of plant material, the percentage of extractives is very low (one percent), but the extraction ratio is extremely high (100:1). Such "high strength" extracts can only be achieved by using more selective, less polar solvents that will only extract specific constituents or a particular fraction of the plant's constituents. Thus, while such products have the appearance of "high potency," they contain only a narrow range of the constituents and are quite possibility lacking in medicinal value. Furthermore, the remaining plant material or marc can then be extracted with more polar solvents to produce an extract that will contains many of the typical constituents. In this manner, one batch of plant material can yield two fraudulent products: a "high strength" extract and a "standardized" extract (Leung, 2001).

Marker compounds are one or more constituents that occur naturally in the botanical material and that are selected for special attention by a researcher or manufacturer

(Eisner, 2001). The amounts of marker compounds as well as the marker compound(s) themselves are often chosen arbitrarily. This selection may be based upon a variety of different factors such as:

• stability of the constituent(s)
• technical ease of analysis
• amount of time and cost of analysis
• utility in confirming identification of the botanical
• potential relevance to therapeutic effect(s)
• indicator of product quality or stability
• previous use by other manufacturers or researchers

Markers are not necessarily "active" compounds. The "actives" may be unknown or the active compounds may be highly unstable or extremely difficult/expensive to analyse. Markers may be chosen to help ensure the correct species identity (e.g., echinacoside for *Echinacea angustifolia*) or the correct chemotype (parthenolide for Feverfew, *Tanacetum parthenium*). Ubiquitous plant constituents such as flavonoids or ferulic acid may be used as indicators of product quality during manufacture or product stability during storage. In some cases, more than one constituent or more than one class of constituents may be used as marker compounds. This may reflect analytical difficulties, the evolution of our scientific knowledge/technical capacity or markers used for different purposes.

As per WHO/EC definition the "active ingredient" is the whole herb or herbal preparation in its entirety. European experts have adopted a new set of terminology that describes and differentiates the various roles of marker compounds very clearly. These terms are active principle(s), active marker(s), analytical marker(s) and negative marker(s). Active principles are compounds with known pharmacological activity that are chemically well defined and generally accepted as the major contributors to the therapeutic effect. Only a very few herbs fall into this category where the potency of the product may be assumed to highly correlate with the content of active principles, thereby justifying adjustments in their content. The herbs for which active markers are known constitute a somewhat larger group. Active markers are pharmacologically relevant, chemically defined constituents that contribute to efficacy, but for which proof that they

are alone responsible for clinical efficacy is still lacking. The majority of herbs fall into the third category namely, herbs for which neither active principles nor active markers are known. In these cases, characteristic compounds or major constituents may be used as analytical markers for which content ranges may be specified. Negative markers are undesirable constituents such as allergens, toxins, or compounds that interfere with bioavailability. Negative markers may be used to screen for the presence of toxic botanicals or undesirable botanical varieties or chemical races, as well as unwanted constituents.

Based upon the current scientific knowledge, compounds with demonstrated *in vitro* activity are usually chosen as markers, although there may be other, unidentified, constituents that play a more important role in determining potency. In most cases, the targeted amount of marker compound is arbitrarily chosen, often based upon the average content of that marker in the raw material or semi-purified extract. The selection and use of markers are thus unregulated and somewhat haphazard. There are numerous discrepancies between brands, both in terms of the markers chosen and the targeted amount of marker. For example, *Panax ginseng* products are claimed to have been standardized to contain anywhere from seven to 70 percent ginsenosides. Kava (*Piper methysticum*) products are claimed to contain anywhere from 30 to 70 percent kavalactones. Similarly, Milk thistle (*Silybum marianum*) products vary in their claimed "standardized" marker content from 30 to 80 percent silymarin or silybin.

Some *Echinacea purpurea* products are standardized to specific citric acid content, while others are standardized to "total phenolic" content. From the scientific perspective, standardization to the total phenolic content is absurd for several reasons. Phenolics are an extremely broad and ill defined class of compounds that potentially encompasses almost half of all plant constituents. For example, chlorogenic acid is a ubiquitous plant constituent; and chlorogenic acid does not have immunostimulant activity. Standardizing to "total phenolics" is, therefore, meaningless, both in terms of producing a consistent product and in terms of potential efficacy. But for the unwary consumer, a product containing four percent total phenolics would to likely appear to be a much more 'potent'

than one containing one percent cichoric acid. While pharmacologically active or useful analytical markers have been identified for most (but not all) of the top selling herbs, markers have not been identified for the vast majority of the 3,000 botanicals commonly found in commerce. It is also difficult to develop cost-effective validated analytical methods for standardization.

Conclusion

The standardization, especially in terms of marker content claims, has been dominant in the public eye, although the concerns raised in the media may be an artefact caused by the wide variations in the methods used to assess marker content. In response to this controversy, industry-wide adoption of validated methods and certification of product quality have been the primary focus of many stakeholder discussions. While marker content is an important issue, some may lose sight of the fact that one has to deal with the plant first of all. In our words chemical analysis is moot if one does not have the right plant or if the plant material is not pure. The industry's fixation on marker content also facilitates fraudulent practices. The issues of methods, method validation and implementation also arise in relation to identity and purity research. In the case of identity testing, there is also a significant gap between the best scientific approach and the methods used by the industry. In the case of purity testing, there is a need for some basic research to determine whether the standard purity tests are reliable in detecting impurities in botanicals, especially finished products. Three other cross cutting themes that have emerged are the need for authenticated reference materials, national quality standards, and pharmacognosy education and training.

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