

Standardization of Herbal Medicinal Products

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Abstract

Consumers and health professionals alike are justifiably apprehensive about the quality of commercial herbal medicines, classified as “dietary supplements” in the United States. North America lacks any governmentally administered program for controlling the identity and quality of botanically-sourced raw material and plant-based commercial products. The choice of an herbal product from the plethora of competing brands is essentially an act of faith in the ethical integrity and scientific competence of the grower/supplier/fabricator/manufacturer continuum. It is only through great effort that consumers can learn which companies are scientifically and technically competent, experienced with the preparation of particular phytomedicines, and whose products are supported by clinical and other experimental data. Physicians who wish to use botanical medicines want to be assured of consistent high quality, efficacious products, and comparable responses from the same dose of an herbal product. However, with herbal products, the identity of the plant’s active principle(s) is/are rarely clearly established. Herbs contain hundreds of compounds, often ranging between extremes of hydrophilicity and lipohilicity. In herbal medicine, an herb’s actions often are recognized long before mechanism of action and active principles are appreciated. Often, numerous constituents are active to different degrees and in various respects. There is relatively little research in this complex area; characteristically, advances in research cause emphasis to shift among the wide variety of classes of compounds, as well as their individual components. Extensive chemical characterization of clinically efficacious preparations appears to be currently the only sensible path towards establishing a reliable basis for quality control and advancing the expectation of consistent pharmacological response. The development of convenient reliable bioassays, correlated with clinical response, should also be pursued to complement chemical profiling.

INTRODUCTION

Standardization, where botanicals are concerned, is almost universally work in progress. Even among the most extensively characterized and researched plant preparations, such as ginkgo leaf extract, still need to be explored to answer nagging questions concerning details of mechanism of action and phytoequivalence (Sticher, 1993). Examples of plants of which the active principles are known are relatively rare. Notable among popular remedies are the laxative sennosides of senna leaf, aescin for venous insufficiency from horse chestnut seed, hepatoprotective silibinin, the flavolignan constituent of milk thistle fruit, the anti-nauseant gingerols from ginger, and the anti-anxiety kavalactones of kava rhizome. When the active principles chiefly responsible for the desired therapeutic effect are known, the levels of such constituents may be adjusted by blending different lots of raw material, whether whole herb or extract. The highest aim of standardization is obviously to provide a product of consistent high quality which reliably delivers a health benefit. In the vast majority of cases, however, active principles are either totally unknown or are not well defined. As a consequence, the herbal preparation in its entirety is regarded as the medicine. In most cases, therefore, one has to rely on chemical markers, preferably highly characteristic of the plant and, if even not significantly contributory to its therapeutic effect, at least correlated with it. In Europe, four categories of constituents relevant to standardization are widely recognized (Busse, 2000):

1. Constituents with known clinical activity (active principles)
2. Constituents with known pharmacological activity or which otherwise contribute to efficacy (active markers)
3. Constituents relevant for quality control (analytical – inactive-markers)
4. Constituents with potential negative impact (negative markers, e.g. allergens, toxins)

Examples of active markers are the terpene trilactones (ginkgolides and bilobalide) and flavonol glycosides of ginkgo, and hypericin and hyperforin from St. John's wort. Hyperforin, the phloroglucinol derivative, was formerly regarded as a significant contributor to the plants anti-depressant action, but is currently in decline of favour – a fate earlier suffered by the dianthrone hypericin (Busse, 2000). Parthenolide, the sesquiterpene lactone constituent of feverfew, once thought to be responsible for the anti-migraine activity of whole leaf preparations exhibits a wide range of in vitro biological activities which are apparently irrelevant to its in vivo anti-migraine effect (Awang, 1998): a 90 % ethanolic extract of the leaf, amply charged with parthenolide, was found to be ineffective (De Weerd et al, 1996). In the category of inactive or weakly active markers are two representatives from echinacea. Echinacoside, the caffeic acid derivative formerly used to standardize *Echinacea angustifolia* and *E. pallida* preparations show no immunostimulatory effects, regarded responsible for echinacea's beneficial influence on cold and flu symptoms, as well as upper respiratory tract infections; the isomeric pair of dodecatetraenoic isobutylamides which dominate the alkamide fraction of *E. purpurea* root exhibit only weak phagocytotic activity and clearly are not significant contributors to the root's immunostimulant activity (Awang, 2000). Negative markers are unwanted constituents, such as allergens and toxins, chemicals which ought not to be present in the botanical or which affect absorption of the active principles; neurotoxic thujones from tansy, ginkgolic acids from ginkgo, and hepatotoxic pyrrolizidine alkaloids present in numerous herbs which have contaminated benign herbs, are examples of negative markers.

RESULTS AND DISCUSSION

Standardization based on a single or small number of chemical markers or classes of compounds serve mainly to promote quality control and batch-to-batch consistency – given the correct botanical identity and part of the plant, cultivated under proper conditions, harvested at the appropriate state of maturity, handled, processed and stored properly. The presence of established levels of a few chemical markers is no guarantee of a botanical preparation's potency. Potency is a biological term reflective of the ability of a preparation to produce a specific therapeutic response. Unless the product has been assayed for biological activity and that activity has been demonstrated to relate to the concentration and therapeutic potential of the product, claims of potency, such as 'guaranteed potency' are inappropriate. Potency indicating bioassays are extremely rare and this area would seem to be the most promising direction for development of more reliably efficacious herbal medicines (Awang and Bejar, 2001).

At the present time, however, the most useful complement to a standardized manufacturing process is to characterize several constituents or groups of constituents and to define suitable ranges. In addition, semi-quantitative finger-prints obtained by high performance liquid chromatography (HPLC), gas chromatography (GC), thin-layer chromatography (TLC) or other suitable techniques can provide further assurance of consistent chemical composition – or reveal significant departure from characteristic profiles, which could indicate poor quality, substitution, adulteration, contamination or degradation.

As research advances towards elucidation of the mechanisms of action and active principles of herbal medicines, panels of selected bioassays reflecting the current state of understanding of specific clinical domains, should reinforce chemical characterization of herbal products.

Beyond all of this, there is a dire need, particularly in North America, for the

establishment of certification processes for assurance of the botanical identity of commercial plant products, and for a program of periodic analytical testing of marketed materials for quality and strength. These programs ought to be governmentally administered in certified laboratories using validated analytical methods. That would obviously be a vast improvement over the practice in recent years of consumer and media organizations purchasing products off commercial shelves and shopping around for commercial analytical laboratories of questionable competence. The analytical results of such sorties are usually reported in the press and TV with great fanfare by scientifically unsophisticated reporters and TV personalities, largely incapable of making proper scientific evaluations of the analytical data. The recent report of finding colchicine in ginkgo and echinacea products, and warning of danger to pregnant women, demonstrates that even academic researchers, not versed in medicinal plant science, can commit stupendous gaffes (Awang et al, 2001).

CONCLUSION

The numerous examples of commercial product variability (8) emphasize the need for continued effort towards more meaningful and effective standardization of herbal medicines, as well as regulatory programs for ensuring proper botanical identity, quality and strength of commercial products.

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Tables

Table 1. Some prominent herbs and associated chemical constituents used for standardization.

<u>Plant material</u>	<u>Constituent</u>
Echinacea	
<i>E. angustifolia</i>	Phenolics [cichoric acid (AM) & echninacoside (ANM)]
<i>E. pallida</i>	Isobutylamides [dodecatetraenoic (ANM)]
<i>E. purpurea</i>	
Feverfew	
<i>Tanacetum parthenium</i>	Parthenolide (ANM)
Ginger	
<i>Zingiber officinale</i>	Gingerols, shogaols (AP)
Ginkgo	
<i>Ginkgo biloba</i>	Ginkgolides, flavonol glycosides (AP, AM)
Ginseng	
<i>Panax ginseng</i>	Ginsenosides (AP)
<i>P. quinquefolius</i>	
Horse chestnut	
<i>Aesculus hippocastanum</i>	Aescin (AP)
Kava	
<i>Piper methysticum</i>	Kavalactones (AP)
Milk thistle	
<i>Silybum marianum</i>	Silymarin (AP)
St. John's wort	
<i>Hypericum perforatum</i>	Hypericin, hyperforin (AM)
Senna	
<i>Cassia acutifolia</i>	Sennosides (AP)
<i>C. angustifolia</i>	
Valerian	
<i>Valeriana officinalis</i>	Valerenic acids (AM)

AM – Active Marker; ANM – Analytical (Inactive) Marker; AP – Active Principle