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# Issues related to botanicals

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**Abstract**

Herbal product studies cannot be considered scientifically valid if the product tested was not authenticated and characterized in order to ensure reproducibility in the manufacturing of the product in question. Many studies refer to the use of standardized material, but in reality they are referring to chemical standardization. While chemical standardization is important, its utility is limited when the starting material is not well characterized botanically. Although the resulting studies are sound with respect to the actual product tested, adequate authentication of the product cannot be compared to other products on the market. Also, a comparison of one study to another cannot be made due to inconsistencies in the identity of the botanical matrix. The tools needed for authentication of the field plant material also depend on the plant and process involved. This could be as straightforward as botanical/morphological identification or as elaborate as genetic or chemical profiling. Authenticated raw material is the basic starting point for the development of a botanical product. However, harvesting, storing, processing and formulating methods may dramatically affect the quality and consistency of the final product by altering the desired marker components or by increasing the possibility of unwanted contaminants. Thus, validated methods to ensure quality control in manufacturing and storage are required tools for optimal efficacy and safety of the products. These controls are also critical for the evaluation of pharmacological, toxicological and clinical studies of the botanical supplements.


*Keywords:* Botanicals; Quality; Safety and efficacy

## Introduction

From time immemorial plants and natural products have provided solutions to many difficult questions the human race has faced. Nature has provided prescriptions for various diseases. These treatments which were developed hundreds of generations ago and then passed on to today's generation have become known as traditional medicine (TRM). The human race is greatly indebted to the countless anonymous authors who compiled the treatises of the Chinese, Ayurvedic and other systems of traditional medicine, as well as the untold scribes and knowledgeable shamans who passed on their locally valued information in a more personal manner. According to a World Health Organization (WHO) estimate, as high as 80% of the population in developing countries depend on traditional and herbal medicines as their primary source of health care (WHO, 2002). Over the past decade, there has been an increased global interest in traditional systems of medicine and herbal medicinal products. In part, this surge has been due to the rare or non-existent access to modern medicine in developing countries as well as the acceptance of herbal medicines by large populations of people in affluent nations. In developed countries, non-conventional medical modalities, also designated as complementary and alternative medicine (CAM), are often used concomitantly with conventional medicine. The popularity of CAM in the USA is reflected in a survey, which showed its use increased from 34% in 1990 to 42% of adults in 1997 (Eisenberg et al., 1998). The same survey showed that American consumers spent $27 billion on alternative treatments, and an estimated $5.1 billion on herbal medicines in 1997 (Eisenberg et al., 1998). In the same year, the global market for herbal products was estimated to be approximately $20 billion (Dev, 1997, 1999).

Integration of herbal medicine can only be accomplished through scientific research, which must take into account the interrelated issues of quality, efficacy and safety. Quality is a paramount and complex issue when dealing with botanicals. One of the most difficult challenges for any company in the herbal industry is being able to consistently formulate a product,

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which will deliver the promised physiological effect. One of the most popular practices followed by herbal industry for standardization is to identify and standardize a particular "marker compound" which is believed to be responsible for the physiological effect to an acceptable percentage (Cardellina, 2002). However, when it comes to the percentage of the markers, different companies have different yardsticks. The percentage of a particular marker for a particular herb varies from product to product in some cases batch to batch from the same company. The following are some of the examples.

A recent study on selected commercial ginseng products prepared from *Panax ginseng*, *Panax quinquefolius* and *Eleutherococcus senticosus* marketed as botanical supplements in North America in the 1995–1998 period showed that the ginsenoside contents of 232 *P. ginseng* and 81 *P. quinquefolius* products ranged from 0.00% to 13.54% and from 0.009% to 8.00%, respectively, and that ca. 26% of these products did not meet label claims (Fitzloff et al., 1998; Awang et al., 1999). The eleutherosides B and E content of eleuthero root powder and other formulated extract products also showed large variation (Fitzloff et al., 1998; Awang et al., 1999). Studies on the quality of St. John's Wort (*Hypericum perforatum*) products showed hypericin content ranging from 22% to 140% of label claim, when analyzed using an official (USP) spectrophotometric procedure (Monmaney, 1998), and from 47% to 165% employing an HPLC method (Constantine and Karchesy, 1999). Similarly, silymarin was detected at 58–116% of labeled claim (Schulz et al., 1997). Aside from the variation in the chemical content of herbal medicine, there can also be pharmaceutical quality differences in these products. In a dissolution and bioequivalent study of nine silymarin products, three yielded 100%, 50%, and 0% of silymarin after one hour under official dissolution study conditions. A bioequivalence study of three of these products showed that the bioavailability of one product was 2-fold greater than the other two preparations (Schulz et al., 1997). The quality of these preparations is primarily affected by several factors. A number of intrinsic as well as extrinsic influences which greatly affect botanical quality have been analyzed to date: species differences, organ specificity, diurnal and seasonal variation, environment, field collection and cultivation methods, contamination, substitution, adulteration, and processing and manufacturing practices (Reichling and Saller, 1998; Simon, 1999; McChesney, 1999; Flaster, 1999; Busse, 1999). In order to achieve a quality product consistently one has to address all the above issues.

The first step towards product quality involves analysis of the herb itself. Botanicals are sold based on chemical components/markers and the variation of chemical constituent can be influenced by environmental factors or genetics. St. John's Wort, *H. perforatum*, is one case where genetic influence has affected the concentration of hypericin in different populations. The narrow leafed populations exhibited a greater concentration of hypericin than the broader leafed variety (Southwell and Campbell, 1991; Campbell et al., 1997). The location of the population has also been shown to affect chemical concentration such as in the steroidal saponins in *Tribulus terrestris* from Bulgaria, India and China (Ganzera et al., 2001a), in the lactones in *Piper methysticum* from Hawaii, Tonga, Fiji and Samoa (Ganzera and Khan, 1999) and in the aristolochic acid I concentration in *Asarum canedense* from the Eastern and Western states of the US (Schaneberg et al., 2002). Genetic influences have also been studied by comparing wild and domesticated populations. In general, both qualitative and quantitative variations of phytochemicals are greater in wild than in domesticated populations of the same species. This variation in phytochemicals was shown in various plant studies such as on artemisinin, the antimalarial agent, in *Artemisia annua* (Reichling and Saller, 1998; ElSohly et al., 1987); on michellamine B, a compound with in vitro anti-HIV activity, in *Ancistrocladus korupensis* (Reichling and Saller, 1998); and on the essential oil composition of *Ocimum basilicum* (Reichling and Saller, 1998), and the podophyllotoxin content in *Podophyllum peltatum* (Canel et al., 2001). Also, the secondary chemical constituents of medicinal plants differ from species to species within a genus as demonstrated by the presence of structurally different alkylamides in the roots of *Echinacea angustifolia* and *Echinacea purpurea,* and by their total absence in *Echinacea pallida* (Bauer, 1998; Bauer and Wagner, 1991) and the saponins in *Astragalus membranaceus*, *Astragalus oleifolius* and *Astragalus melanophrurius* (Ganzera et al., 2001b). Thus, to insure chemical uniformity, it is necessary that the starting plant material for the manufacture of botanicals be accurately identified and authenticated by their scientific names (Latin binomial) in the form of a voucher specimen. The need for the scientific name is important because a common name is inadequate as it often refers to more than one species. Such as in the case of *Ephedra*, Ma Huang is considered the common name for *Ephedra sinica*, *Ephedra equisetina* or *Ephedra intermedia*. Even when plants may not have the same common name, problems still arise when common names are similar. This can lead to accidental substitution of a safe species by a toxic species. An example would be the nontoxic *Sinomenium acutum* (Boui) versus the toxic *Aristolochia fangchi* (Kou-boui) (Hashimoto et al., 1999). Chemical fingerprinting of species within a genus is one possible method for the authentication of plant material. Recently, a HPLC method was reported which could distinguish between 90 species of *Passiflora* (Abourashed et al., 2002).

Another factor involves plant organ specificity in which the site of biosynthesis and the site of accumulation and storage are normally different. Chemical biosynthesis usually takes place in the leaves, and then the chemical is transported through the stems to the roots for storage. Although accumulation and storage can also take place in the leaves, it is to a much lower extent, and storage is very infrequently in the stems. An example of site-specific accumulation, as well as species specificity, is that of the compounds considered responsible for the immunostimulant effect of *Echinacea* species. These compounds encompass five groups of chemicals: caffeic acid derivatives, alkylamides, polyacetylenes (ketodialkenes and ketodialkynes), glycoproteins and polysaccharides. As indicated above, alkylamides are found in the roots of *E. angustifolia* and *E. purpurea,* but they are structurally different; and are totally absent in *E. pallida* roots. Polyacetylenes, on the other hand, are present