

REVIEW

Herbal Medicine: Safety and Quality Concerns

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ABSTRACT

Herbal products are complex mixtures of organic chemicals that may come from any raw or processed part of a plant or the parts themselves, such as leaves, stem, flowers, roots and seeds. It is estimated that 37% of sales of the world's pharmaceutical products originate from natural raw material. It appears that dependence upon herbal now are widely acknowledged by the general public and endorsed by the medical profession at large. Current law defined herbs as dietary supplement. In this case, the evidence of efficacy and demonstration of safety not a vital requirement as pharmaceutical drugs. Aligned with increase in worldwide consumption, the safety of herbal medicine is subject of concern. Although herbs are often perceived as “natural”, “green” and “back to nature” rhetoric, many side effects have been reported owing to contaminants, adulteration, or interaction with other drugs. The socio-economic changes plus the technological advances, commercial factors, consumers' preferences and changing lifestyles have influenced the way herbal drug are being manufactured and distributed. A various range of botanical medicine is now available as over-the-counter (OTC) products. Thus, just like pharmaceutical industry, it has become utmost importance to assure quality, safety and efficacy of herbal product through the whole manufacturing process.

Keywords: Herbal medicine, quality control, herbal safety

ABSTRAK

Produk herba merupakan campuran bahan kimia organik yang berkemungkinan dari sebarang bahan mentah atau yang telah diproses daripada bahagian tumbuhan atau tumbuhan itu sendiri seperti daun, batang, bunga, akar atau biji. Jangkaan menunjukkan bahawa 37% jualan produk farmaseutikal adalah berasal dari bahan mentah semulajadi. Hakikat kepada kebergantungan kepada herba pada masa kini telah diakui oleh orang ramai dan juga diakui oleh ahli perubatan secara meluas. Undang-undang yang sedia ada mentakrifkan herba sebagai makanan sampingan. Dalam hal ini, bukti keberkesanan and penerangan tentang keselamatan tidak menjadi keperluan utama sepertimana ubatan farmaseutikal. Sejajar dengan pertambahan penggunaan seluruh dunia, keselamatan penggunaan ubatan herba perlu diberi perhatian. Walaupun herba selalu dianggap retorik “semulajadi”, “hijau” dan “kembali ke alam semulajadi”, banyak kesan sampingan telah dilaporkan akibat dari pencemaran, pencampuran, atau interaksi dengan ubat yang lain. Perubahan sosio-ekonomi ditambah dengan perkembangan teknologi, factor komersil, pilihan pengguna dan perubahan gaya hidup telah mempengaruhi cara ubatan herba dihasilkan dan diedar. Berbagai rangkaian ubatan botanikal masakini boleh didapati sebagai produk *over-the-counter* (OTC). Justeru itu, sepertimana industri farmaseutikal, adalah penting sekali dipastikan kualiti, keselamatan dan keberkesanan produk herba dari mula hingga akhir proses penghasilan.

Kata kunci: ubatan herba, kawalan kualiti, keselamatan herba

INTRODUCTION

An herb constitutes of any form of a plant part or plant products, such as root, stem, leaves, resin, seed, flowers, bark and fruits. Written records of the use of herbal medicine dated more than 5,000 years ago (Swerdlow, 2000). As a matter of fact, herbal medicine was the primary source of medicine back then. It has been estimated that 25% of modern medicine are derived from plants first used traditionally (Bent, 2008). In recent decades, complementary and alternative medicine including herbal medicine gained more attention.

The popularity of herbal usage has been promoted by; i) the development of new diseases, with severe complications and no appropriate treatment available, ii) the belief that herbal remedies are safe, iii) the idea of natural can only be good, iv) the escalation of the research and development of traditional herbal medicine system, and v) the market expansion of health products including herbal medicine. The development of this market has been linked to several drivers, firstly, consumers are increasingly taking charge of their health and therefore, there is a public demand for health- related products. Secondly, the scientific understanding of the

beneficial health impact of bioactive components of foods and dietary supplements has improved significantly and has been extensively communicated to the public. Thirdly, the progress achieved in the field of production and conservation of herbal medicines. Today, the possibility of cultivating medicinal plants, sometimes genetically improved (Goldstein and Thomas, 2004), enables to introduce on the market plants, which are rich in desirable active compounds.

THE CHALLENGES FOR QUALITY CONTROL OF HERBAL MEDICINE

The Plant Physiology

One of the most intriguing aspects of medicinal plant physiology is the characterization of those metabolites that make the species unique, commonly known as secondary metabolites. Secondary metabolites are bioactive molecules, which provide the plant with defence mechanisms to survive herbivores, environmental stress, disease or competition and these compounds may effect the growth and development of other organisms (Seigler, 1996). Each individual species has unique profile of secondary metabolites and in this pool of biochemical that commonly contains the medicinally active components. The mode of action of many of these active components includes the ability to inhibit cell division, to modify DNA and RNA and to inhibit specific enzymes. In addition, plant secondary metabolites also exhibit antiparasitism, antifungal and antibacterial properties (Seigler, 1996; Murch *et al.*, 2001).

However, it is known that the therapeutic efficacy of herbal medicine is not always determined by a single group of compound (Cappasso *et al.*, 2000; Constantine & Karchesy, 1998; Seigler, 1996). For example, St. John's wort preparation contain a complex balance of more than two dozen bioactive compounds including naphthodianthrones (hypericin, psedohypericin, isohypericin, protohypericin), flavonoids (amentoflavone, hyperin, kaempferol, luteolin, myricetin, quercetin), phloroglucinols (hyperforin, adhyperforin, hyperoside, leucocyanidin), antioxidants, tannins, coumarins, xanthones, essential oils, amino acids, organic acids and carotenoids (Miller, 1998). These complex mixtures of bioactive molecules, attributable to several compounds working in a synergistic manner and this situation become even more complicated for medicinal plant preparations that contain more than one species. Figure 1 shows example multi-herbal preparation for antidiabetic botanical drug.

MULTI-HERBAL PREPARATION



Figure 1 Example of the ingredient of multi-herbal preparation

Identifying the Bioactive Constituents

As indicated earlier, the efficacy of medicinal plant species may be attributed to a single compound or a multitude compounds or may be a result of synergistic interaction of many metabolites within the herbal medicine preparation. In an attempt to handle this issue, Drug Identification Numbers (DIN) has been issued by the United State Food Drug Association (USFDA) for various whole plant preparations on the basis of standard concentration of a medicinal compound. For example, feverfew is given the DIN based on a minimal concentration of 0.2% of parthenolide (Murch *et al.*, 1997). However, in an earlier study, it was revealed that

parthenolide alone did not provide the therapeutic effect of feverfew (De Weerd *et al.*, 1996) and therefore the products that only have been standardized to specific concentration of a marker compound that may have little relevance for the treatment dose. Another problem that can arise with whole plant preparation is the potential occurrence of high levels of unidentified metabolites that led to the adverse effects or toxicity when consumed alone or with other phytomedicine or pharmaceuticals. Fig. 2 show the example spectra of thin layer chromatography densitogram of complex constituents in *Orthosiphon stamineus* extracts, a popular herb used to treat kidney stone, that possesses diuretic as well as many other pharmacological activities.

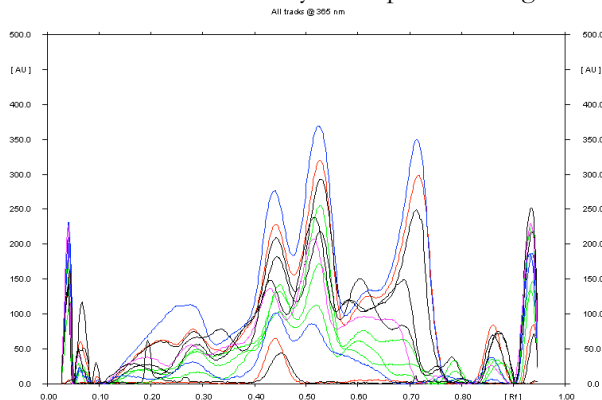


Figure 2 Spectra of thin layer chromatography densitogram of *Orthosiphon stamineus* extracts

Variability in Individual Plants

The chemical constituents of medicinal plants can be affected by several ways including genetic difference that are not obvious morphologically and the ontogeny of the individual plant or population that affects secondary metabolites (Foster, 1989). Selection has to be done to identify the superior individuals within the population and identify chemicals that contribute to the variability in medicinal plant products. Example of plant that has multiple varieties is *Ficus deltoidea* Jack, an herb that normally is consumed to reduce high blood sugar and typical specimens of the varieties and the problems posed by a diverse variety is shown in Fig. 3.

Adulteration and Deterioration

The adulteration of raw material may take place either deliberately or unintentionally. They are two types of adulteration; i) admixture, which is the addition of one plant to another, for example, inclusion of other parts for example mixing the root with stem, or collection of two similar species and ii) substitution, which the addition of entirely different material of what it is originally required.

Substitution with non-active or very rarely with more toxic herbs may occur erroneously, when the herb is incorrectly identified, or deliberately for economic reasons when a cheaper herbs is supplied to replace a safer, more expensive one. This scenario can cause serious implication to human health. In one example, misidentified plant species in an herbal diet product resulted in the loss of renal function through irreversible interstitial fibrosis in more than 100 patients (Betz, 1998). In another example, about 2700 kg of contaminated raw plant material labelled as plantain was imported, processed and distributed over period of approximately two years in the United States. The plant material contained *Digitalis lanata* and ingestion of the processed products resulted in toxic level of serum digoxin in patients (Slifman *et al.*, 1998).

Furthermore, confusion between related species with similar morphology but different profiles of bioactive molecules can pose additional problems for preparation of plant-based medicines. For instance, the three primary species of *Echinacea*, namely *E. purpurea*, *E. angustifolia* and *E. pallida* are frequently confused. *Echinacea* products may also be contaminated with other species, *Parthenium interifolium* (Family: Compositae). These contaminations can result in significant variation in profiles of bioactive molecules of the medicinal plant preparations due to the presence of species-specific compounds. Even for the same species of plant, physical appearance can be varied as shown in Fig. 5.

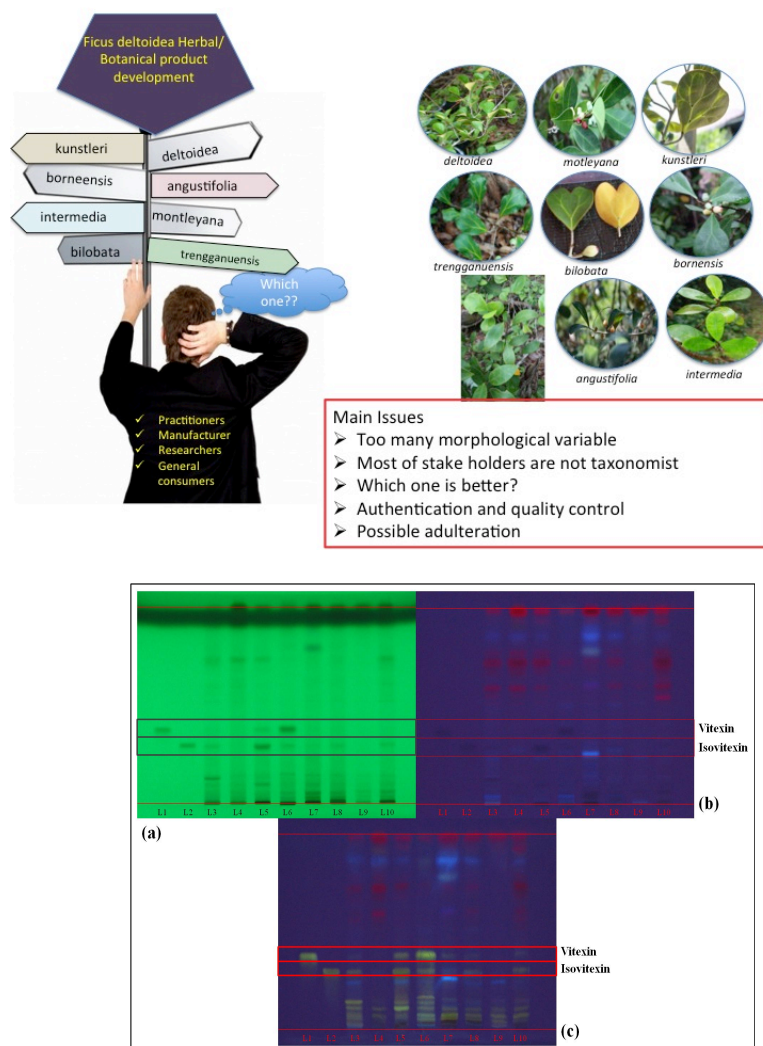


Figure 3 *Ficus deltoidea* Jack. An herb with multiple varieties and complex chemical compounds and vary concentration of marker compounds. a-c is thin layer chromatograms with different detection methods.

Adulteration also can take place during the production process. Adulteration with synthetic drug is a major problem with herbal medicine. The clinical consequences can be serious and sometimes life threatening. This is especially so when patients are on similar medications, with potential interactions or when patients have other predisposing medical conditions. Vanhalen *et al.* (1994) reported one of the classic example of substitution and adulteration of conventional drugs in herbal medication, where the cluster of cases of rapidly progressive interstitial nephritis was reported in Belgium. Following investigation, this problem was attributed to the substitution of *Aristolochia fangchi* instead of the Chinese medicinal herb *Stephania tetrandra* in a combined slimming regimen that included some conventional medications. Most of the cases were involved young women of whom some developed irreversible end-stage renal failure and/or the urinary tract infection. These incidences highlight the importance of detecting the presence of any synthetic drug in herbal medicine to ensure their safety. Ministry of Health via Pharmaceutical Services Division has listed the products that contain banned substances (Table 1).

Deterioration can takes place when improper management occurred during storage. Spoilage is a substandard condition produced by microbial or other pest infestation, making product unfit for consumption. According to Bilia *et al.* (2001), stability is defined as the time during the material retains its integrity in terms of quality and chemical identity. Stability can be affected by environmental factors such as air temperature, pH, light and humidity, which can have dramatic effects on some constituents; therefore stability testing is very important to determine the rate of deterioration. Dried herbs are more prone to the contamination by bacteria spores and

molds, which present in the air. A combination of humidity and temperature caused rapid growth of bacteria and molds. In such conditions, the raw material should not further processed.

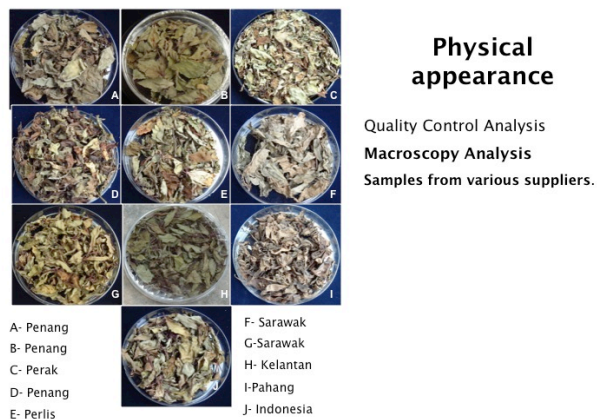


Figure 5 Physical appearances of raw materials of *Orthosiphon stamineus* from different suppliers.

Table 1 Some of Products Containing Banned Substances (Pharmaceutical Services, Malaysian Ministry of Health)

Product Name	Type	Banned Substance
357 Nasal Spray	Traditional Health	Dexamethasone
Acai Berry ABC	Traditional Health	Sibutramine
Beautiful Slim Body	Traditional Health	Sibutramine
Kopi Jantan Traditional	Drink	Analog Sildenafil
Maajun Tenaga Herba-Ubi Jaga	Traditional Health	Dexamethasone
Madu Adunan Herba	Traditional Health	Dexamethasone
Natasya Krim Herba	Cosmetic	Hydroquinone and Tretinoin

Contamination of Plant Materials

Field-grown crops, by nature, are exposed to a variety of bacteria, pests and fungi. These are the pathogens, which, if not properly managed, will affect the level of medicinal metabolites in various species. For example, *Septoria spp* infection was shown to reduce the concentration of active constituents of *Digitalis lanata* (Bernath, 1986). Weed can inhibit the establishment and growth of crops and also a source of contamination when the plant material is harvested conventionally. Herbicide also can cause contamination if not used properly. Overuse of herbicide can affect the secondary metabolite production and therefore the profile of bioactive molecules may be altered (Murch *et al.*, 2001).

Heavy metal contamination is a result of environment contamination and cause enormous effect to human health when exceed the minimum allowed level. Study indicated that the inheritance nature of some plant species to uptake and accumulate organic and inorganic from polluted soil (Peralta-Videa *et al.*, 2002). A review by Koh & Woo (2000) stated that excessive toxic heavy metals and undeclared drugs in Chinese proprietary medicines in Singapore had been detected between 1990 and 1997. The present of unusual high concentrations of toxic heavy metal could lead to fatality if consumed (Chan, 2003).

CONCLUSION

Modern and traditional health care often exist side by side but seldom cooperate, despite the important contribution that herbal medicine makes to primary health care. This is mostly due to the view that it has no scientific basis. Taking into account the complexity of herbal drugs and their inherent biological variation, it turns imperative to evaluate their safety, quality and efficacy. The issue of safety, quality and efficacy are the real concern and standardization has becomes an important matter to consider when herbal medicine is concern. Serious consideration of herbal medicine as an alternative or complementary form of medical treatment requires rigorous examination, which involves fundamental issues as listed below:

- *Source Material.* Each batch of herbs must be properly identified, first by morphology, and then by microscopic examination. The source material also must adhere to the limit of contamination such as foreign material, microbial, heavy metals and other extraneous matter.
- *Standardization.* Standardized herbal product must have a known content of active or marker compounds. Due to the complexity of chemical component in herbal, fingerprint analysis is an acceptable strategy for the assessment of herbal medicine. Chemical fingerprint obtained must be simple, rapid and environmental friendly, which can be an attractive option for regulatory laboratories, testing laboratories and laboratories supporting manufacturing activities.
- *Evidence of efficacy is vital.* However, because the composition of the product varies between manufacturers, evidence of efficacy should be considered to be extract specific. At most, evidence should be extrapolated only to preparations of the same herbs with similar profile of constituents.

There is no country of the world in which one cannot find herbal medicinal products and there is no society, which could claim that it has never used plants as medicine. As we optimistic about the natural healing power of herbs, extra precaution steps should be taken into consideration. Herbal products must be standardized to guarantee the safety, quality and efficacy start from raw material to finish products and batch to batch consistency. Authenticity and homogeneity of herbal products must adhere to strict regimes of Good Agricultural and Collection Practice (GACP), Good Plant Authentication and Identification Practice (GPAIP), Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP). Strict quality assurance is vital in order to achieve highest quality herbals, consistent in efficacy and most importantly to ensure the safety of consumers.

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