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Emerging Trends in the Quality Check of Herbal Medicines, Supplements and 'Botanicals'

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ABSTRACT

Even in modern times, the popularity level of medicinal plants and herbal medicines in therapy is still high. The World Health Organization estimates that 80% of the population in developing countries uses these types of remedies. Even though herbal medicine products are usually perceived as low risk, their potential health risks should be carefully assessed. Several factors can cause the toxicity of herbal medicine products: plant components or metabolites with a toxic potential, adulteration, environmental pollutants (heavy metals, pesticides), or contamination of microorganisms (toxigenic fungi). Their correct evaluation is essential for the patient's safety. The toxicity assessment of herbal medicine combines in vitro and in vivo methods, but in the past decades, several new techniques emerged besides conventional methods. The use of omics has become a valuable research tool for prediction and toxicity evaluation, while DNA sequencing can be used successfully to detect contaminants and adulteration. The use of invertebrate models (*Danio renio* or *Galleria mellonella*) became popular due to the ethical issues associated with vertebrate models. The aim of the present article is to provide an overview of the current trends and methods used to investigate the toxic potential of herbal medicinal products and the challenges in this research field.

keywords: **contamination**; **DNAsequencing**; **genotoxicity**; **omics**; **standardization**

INTRODUCTION

'traditional' use of herbal medicines implies substantial historical use, and this is certainly true for many products that are available as 'traditional herbal medi- cines'. In many developing countries, a large proportion of the population relies on tradi- tional practitioners and their armamentarium of medicinal plants in order to meet health care needs. Although modern medicine may exist side-by-side with such traditional practice, herbal medicines have often maintained their popularity for historical and cultural reasons. Such products have become more widely available commercially, espe- cially in developed countries. In this modern setting, ingredients are sometimes marketed for uses that were never contemplated in the traditional healing systems from which they emerged. An example is the use of ephedra (= Ma huang) for weight loss or athletic performance enhancement (Shaw, 1998). While in some countries, herbal medicines are subject to rigorous manufacturing standards, this is not so everywhere. In Germany, forexample, where herbal products are sold as 'phytomedicines', they are subject to the same criteria for efficacy, safety and quality as are other drug products. In the USA, bycontrast, most herbal products in the marketplace are marketed and regulated as dietary supplements, a product category that does not require pre-approval of products on thebasis of any of these criteria.

The role of herbal medicines in traditional healing

The pharmacological treatment of disease began long ago with the use of herbs (Schulz *et al*., 2001). Methods of folk healing throughout the world commonly used herbs as part of their tradition. Some of these traditions are briefly described below, providing some examples of the array of important healing practices around the worldthat used herbs for this purpose.

Traditional Chinese medicine

Traditional Chinese medicine has been used by Chinese people from ancient times.Although animal and mineral materials have been used, the primary source of remediesis botanical. Of the more than 12 000 items used by traditional healers, about 500 are incommon use (Li, 2000). Botanical products are used only after some kind of processing,

which may include, for example, stir-frying or soaking in vinegar or wine. In clinical practice, traditional diagnosis may be followed by the prescription of a complex and often individualized remedy.

Traditional Chinese medicine is still in common use in China. More than half the population regularly uses traditional remedies, with the highest prevalence of use in rural areas. About 5000 traditional remedies are available in China; they account for approxi- mately one fifth of the entire Chinese pharmaceutical market (Li, 2000).

Japanese traditional medicine

Many herbal remedies found their way from China into the Japanese systems of traditional healing. Herbs native to Japan were classified in the first pharmacopoeia ofJapanese traditional medicine in the ninth century (Saito, 2000).

Indian traditional medicine

Ayurveda is a medical system primarily practised in India that has been known fornearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment (Morgan, 2002).

Introduction of traditional herbal medicines into Europe, the USA andother developed countries

The desire to capture the wisdom of traditional healing systems has led to a resur-gence of interest in herbal medicines (Tyler, 2000), particularly in Europe and North America, where herbal products have been incorporated into so-called 'alternative', 'complementary', 'holistic' or 'integrative' medical systems.

During the latter part of the twentieth century, increasing interest in self-care resulted in an enormous growth in popularity of traditional healing modalities, including the useof herbal remedies; this has been particularly true in the USA. Consumers have reported positive attitudes towards these products, in large part because they believe them to be of 'natural' rather than 'synthetic' origin, they believe that such products are more likely to be safe than are drugs, they are considered part of a healthy lifestyle, and they can helpto avoid unnecessary contact with conventional 'western' medicine.

While centuries of use in traditional settings can be used as testimony that a parti-cular herbal ingredient is effective or safe, several problems must be addressed as theseingredients are incorporated into modern practice.

One problem is that ingredients once used for symptomatic management in tradi- tional healing are now used in developed countries as part of health promotion or disease prevention strategies; thus, acute treatment has been replaced by chronic exposure (e.g., herbal products used for weight loss, Allison *et al.*, 2001). This means that a statementabout 'thousands of years of evidence that a product is safe' may not be valid for the way the product is now being used. This does not expressly mean that an ingredient is unsafe; it does mean that safety in the modern context cannot be assumed.

SOME TRADITIONAL HERBAL MEDICINES

A second problem is that efficacy and effectiveness have rarely been demonstrated using modern scientific investigations. An evidence-based approach to this issue has only recently been implemented, and the results reveal that for most herbal products, considerable gaps in knowledge need to be remedied before one can be convinced about their efficacy.
One of the most difficult issues to contend with in translating traditional herbal practices into conventional 'western' medicine is the individualization of prescriptions containing multiple herbal and other ingredients. There is little incentive for standar- dization of products for a mass market, when the intention has been to provide an indivi- dual prescription. To the small grower or the traditionally trained herbalist, standar- dization means understanding the growth conditions, the time of harvesting, the mannerof extraction or other preparation of material so that a reliable (albeit small amount of)active ingredient can be offered to people. To the manufacturer or distributor of largequantities that will be sold in a supermarket or a health food store, standardization refers to industrial production under defined conditions, using so-called Good ManufacturingPractices (GMP) (Food & Drug Administration, 2002) akin to those used for drug production.In the USA, there is both small-scale and large-scale production of herbal productsand there can be wide variation in their content and quality in the marketplace. Regu-lations in the USA do not yet require that dietary supplement manufacturers adhere to standard manufacturing practices, and so quality is not guaranteed (see Section 3). Thepublic becomes discouraged by reports that products taken from store shelves do notconsistently contain the ingredients — or in the amounts — that are claimed on the label.For herbal products in common use, evidence of efficacy may be based upon tradi- tional use, testimonials, clinical studies, both controlled and uncontrolled, and rando-mized, double-blind, placebo-controlled trials. For the most part, however, there is a lack of systematic clinical studies to support claims.Safety of some herbal ingredients

has been recently called into question, in part because of the identification of adverse events associated with their use and, increasingly,because of the demonstration of clinically relevant interactions between herbs and pres-cription drugs.

Adverse events (stroke, heart attacks, heart-rate irregularities, liver toxicity, seizures, psychoses and death) associated with use of ephedra for weight loss, body-building effects and increased energy or kava-kava (also known as kawa), widely used in Europe and increasingly in Canada to treat anxiety, nervousness, insomnia, pain and muscle tension, for example, have caused some countries to issue regulations restricting or banning these products (e.g. Health Canada Online, 2002a,b). Only a few herbs in common use have been suspected of causing cancer. These include *Aristolochia*, *Rubia tinctorum*, *Morinda officinalis* and *Senecio riddellii*, as discussed in detail below.

Use of Traditional Herbal Medicines in Developed Countries

Origin, type and botanical data

Plants and their secondary metabolite constituents have a long history of use in modern 'western' medicine and in certain systems of traditional medicine, and are thesources of important drugs such as atropine, codeine, digoxin, morphine, quinine and vincristine.

Use of herbal medicines in developed countries has expanded sharply in the latter half of the twentieth century. Monographs on selected herbs are available from a number of sources, including the European Scientific Cooperative on Phytotherapy (ESCOP, 1999), German Commission E (Blumenthal *et al.*, 1998) and the World Health Organi-zation (WHO, 1999). The WHO monographs, for example, describe the herb itself by anumber of criteria (including synonyms and vernacular names) and the herb part commonly used, its geographical distribution, tests used to identify and characterize the herb (including macroscopic and microscopic examination and purity testing), the active principles (when known), dosage forms and dosing, medicinal uses, pharmacology, contra-indications and adverse reactions. Other resources that provide detailed infor- mation about herbal products in current use include the Natural Medicines Compre- hensive Database (Jellin, 2002) and NAPRALERT (NAtural PRoducts ALERT) (2001). Information about other available databases has been published by Bhat (1995).

Medicinal applications, beneficial effects and active components

In some cases, the active principles of plant-derived products have been isolated and characterized, and their mechanisms of action are understood (e.g., ephedrine alkaloidsin some species of *Ephedra*). For many, however, including virtually all of the most common products in the marketplace, such information is incomplete or unavailable. This is in large part due to the complexity of herbal and botanical preparations; they arenot pure compounds. It is also a function of the traditionally-held belief that the syner-gistic combination of several active principles in some herbal preparations is responsible for their beneficial effects.

Trends in use

Data on the global nutrition products industry, in which herbal and botanical productsare often included, are given in Table 1.
Sales of dietary supplement products, including herbal and botanical supplements, in the USA increased dramatically during the 1990s, stimulated in the latter part of the Herbal ingredients used in combination are widely used in Europe, and their assessment is often performed according to specific guidelines. Combinations of herbal and homeopathic ingredients exist in a few countries. Their assessment follows ratherstrict criteria, usually those of a 'full' application procedure. Combinations of herbal ingredients and vitamins are available in many countries.

For herbal medicinal products that have been proposed for non-traditional indi- cations or are modified from their traditional form (e.g., highly processed or special extracts), a full licence is required in most cases, and efficacy has to be proven by clinicalstudies. In several countries, such products are not used.

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Table 1. The global nutrition products industry in 1999, including herbal and botanical products (in millions of US $)

Country	Vitamins/ minerals	Herbs/ botanials	Sports,meal replacement, homeopathy, specialty	Natural[a] foods	Naturalpersonalcare	Functionalfoods[b]	Total
USA	7 070	4 070	4 320	9 470	3 590	16 080	44 520
Europe	5 670	6 690	2 510	8 280	3 660	15 390	42 200
Japan	3 200	2 340	1 280	2 410	2 090	11 830	23 150
Canada	510	380	250	700	330	1 500	3 670
Asia	1 490	3 170	970	710	880	1 450	8 670
Latin America	690	260	250	460	250	360	2 270
Australia and New Zealand	300	190	90	340	140	540	1 600
Eastern Europe and Russian Federation	350	220	250	180	40	269	1 300
Middle East	180	90	60	70	30	140	570
Africa	160	80	70	80	10	120	520
Total global	19 260	17490	9 960	22700	11020	47670	128470

From Nutrition Business Journal (2000), derived from a number of sources. Totals may not add up due to rounding.[a] Natural foods: foods grown or marketed with a focus on the perceived benefits of 'foods derived from natural sources' and that are, tovarying degrees, free of pesticides, additives, preservatives, and refined ingredients

[b] Functional foods: foods fortified with added or concentrated ingredients to improve health and/or performance decade by the Dietary Supplements Health and Education Act of 1994 (DSHEA) (Tyler,2000). This pattern of growth has been replicated elsewhere in the world (Table 2),although more recently, sales of herbal products have apparently experienced a decline.

In the European Union (EU), in general, herbal products for which therapeutic claims are made must be marketed and regulated as drugs, while those that do not make suchclaims may be found in the food or cosmetic categories. Attempts are at present beingmade to harmonize the scientific and regulatory criteria that govern the marketing of herbal products (AESGP, 1998).

Table 2. Trends in the global nutrition products industry,1997–2000 (in millions of US $)

	1997	1998	1999	2000
Vitamins/minerals	18000	18870	19620	20440
Herbs/botanicals	15990	16980	17490	18 070
Sports, meal replacement, homeopathy,specialty	8760	9310	9960	10710
Natural foods[a]	16690	19910	22700	25420
Natural personal care	9620	10280	11020	11850
Functional foods[b]	40320	43940	47670	51480
Total	109380	119 290	128 470	137980

From Nutrition Business Journal (2000), derived from a number of sources[a] Natural foods: foods grown or marketed with a focus on the perceived benefits of 'foods derived from natural sources' and that are, to varying degrees, free of pesticides, additives, preservatives, and refined ingredients[b] Functional foods: foods fortified with added or concentrated ingredients to improve health and/or performance

WHO guidelines for herbal medicines

In 1992, the WHO Regional Office for the Western Pacific invited a group of experts to develop criteria and general principles to guide research work on evaluating herbal medicines (WHO, 1993). This group recognized the importance of herbal medicines tothe health of many people throughout the world, stating: 'A few herbal medicines have withstood scientific testing, but others are used simply for traditional reasons to protect, restore, or improve health. Most herbal medicines still need to be studied scientifically,although the experience obtained from their traditional use over the years should not beignored. As there is not enough evidence produced by common scientific approaches to answer questions of safety and efficacy about most of the herbal medicines now in use,the rational use and further development of herbal medicines will be supported by further appropriate scientific studies of these products, and thus the development of criteria forsuch studies'.

The document covered such topics as developing protocols for clinical trials usingherbal medicines, evaluating herbal medicine research, guidelines for quality specifi- cations of plant materials and preparations, and guidelines for pharmacodynamic and general pharmacological studies of herbal medicines and for toxicity investigations ofherbal medicines.

WHO has also issued Guidelines for the Assessment of Herbal Medicines (WHO,1996). These guidelines defined the basic criteria for the evaluation of quality, safety and efficacy of herbal medicines with the goal of assisting national regulatory authorities,scientific organizations and manufacturers in assessing documentation, submissions and dossiers in respect of such products. It was recommended that such assessments take into account long-term use in the country (over at least several decades), any description in the medical and pharmaceutical literature or similar sources or documentation of knowledge on the application of a herbal medicine, and marketing authorizations for similar products. Although prolonged and apparently uneventful use of a substance usually offers testimony of its safety, investigation of the potential toxicity of naturallyoccurring substances may reveal previously unsuspected problems. It was also recom-mended that regulatory authorities have the authority to respond promptly to new infor- mation on toxicity by withdrawing or limiting the licences of registered products contai- ning suspect substances, or by reclassifying the substances to limit their use to medicalprescription. The guidelines stressed the need for assessment of efficacy including thedetermination of pharmacological and clinical effects of the active ingredients, and labelling which includes a quantitative list of active ingredient(s), dosage, and contra-indications.

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