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ORGANIC AND BIOMOLECULAR CHEMISTRY DIVISION*
SUBCOMMITTEE ON BIOMOLECULAR CHEMISTRY**

PROTOCOLS ON SAFETY, EFFICACY, STANDARDIZATION, AND DOCUMENTATION OF HERBAL MEDICINE

(IUPAC Technical Report)

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Protocols on safety, efficacy, standardization, and documentation of herbal medicine

(IUPAC Technical Report)

Abstract: This Technical Report compiles and analyzes the current scientific knowledge on herbal medicine and highlights the practical ways for ensuring the safety of herbal preparations and evaluating their claimed efficacy. Emphasis has been given to the methods for standardization of herbal medicine and the ways and means for moving forward to achieve the difficult goal of preparing herbal medicines of consistent quality and effects. Pragmatic approaches have been recommended to overcome the difficulties in (i) protecting intellectual property rights (IPR); (ii) producing safe, potent, standardized, and affordable herbal medicine; and (iii) documenting the knowledge base on herbal medicine in an easily accessible format.

Keywords: herbal medicine; safety; efficacy; standardization; documentation; intellectual property rights; task group; IUPAC Organic and Biomolecular Chemistry Division.

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PREFACE

"Health for all" is a dream and a goal which humanity at large shares and strives for. Unfortunately, it has now been proven without doubt that modern pharmaceuticals are and will remain out of reach for a large proportion of the human population for the foreseeable future. This has created an appreciation and a need for the use of other sources of human knowledge to provide common health benefits. Alternative and traditional medicines, largely herbal in nature, are now regarded as important but underutilized tools against disease. The World Health Organization (WHO) recognized this fact in the early 1970s and encouraged governments to effectively utilize local knowledge of herbal medicines for disease prevention and health promotion. Herbal medicines, however, suffer from a range of shortcomings. These include insufficient and unacceptable evidences of safety, efficacy, standardization, and inconsistent production practices.

IUPAC's initiative to sponsor a project to compile protocols and a monograph on *safety, efficacy, standardization, documentation, and intellectual property rights (IPR)* of herbal medicine through a task group is, therefore, a very welcome initiative. Various sections in this document describe the background and current status of the science of herbal medicines, particularly with reference to their safety and efficacy. A section on different approaches to the complex issue of standardization of herbal medicine presents an important aspect of the development of safe and effective herbal medicines. Efforts have also been made to highlight the importance of proper documentation and IPR protection of indigenous knowledge of plant uses for medicinal purposes.

This document is an attempt to compile, in one place, various aspects of the science of herbal medicine in modern times. The draft document was presented at the IUPAC Organic and Biomolecular Chemistry Division meetings in Torino, Italy in August 2007. Although most of the information compiled here is available in various reports, reviews, and monographs, the personal experiences and insight of the contributors should make this report a useful and relevant addition.

1. BACKGROUND

1.1 Introduction

Herbal medicine has become a popular form of healthcare. The consumption of plant-based medicines and other botanicals in the West has increased manifold in recent years. For example, between 1990–2000, an increase of over 380 % in sales in the United States was recorded. Global sales of herbal products, including herbal medicines, is already over USD 10^{11} and is expected to exceed USD 10^{12} in the next 20 years at the present growth rate.

About two centuries ago, our medicinal practices were largely dominated by plant-based medicines. However, the medicinal use of herbs went into a rapid decline in the West when more predictable synthetic drugs were made commonly available. In contrast, many developing nations continued to benefit from the rich knowledge of medical herbalism. For example, Ayurvedic medicine in India, Kampo

medicine in Japan, traditional Chinese medicine (TCM), and Unani medicine in the Middle East and South Asia are still used by a large majority of people.

In the recent era of herbal renaissance, the demand of herbal medicines and other botanicals by Western communities has been increasing steadily, particularly over the past two decades. Figures from the Consumers Association in the United Kingdom suggest an increase in utilization of herbal therapies by their members from one in seven in 1985 to one in four in 1991 [1]. In 1997, figures from the United States suggested that as high as 67.6 % of the population had used complementary and alternative therapy at least once in their lifetime [2]. Australian data on 3027 South Australians found that approximately one in two (52.1 %) had used at least one form of herbal product in the year 2000 and 23.3 % of all respondents had visited at least one herbal practitioner during that year [3]. This study also indicated that 57.2 % of herbal users did not discuss herbal use with their physician. Estimates of the national cost of both herbal medicines and practitioner visits have been placed at approximately 2.3×10^9 Australian dollars annually [3].

In parallel with this trend, TCM, represented by acupuncture and Chinese herbal medicine, is currently being used more widely than ever before in Western countries [4]. In Australia, it has been estimated that there are at least 2.8×10^6 TCM consultations each year, and this alone represents an annual turnover of 84×10^6 Australian dollars within the health economy [5]. Along with herbal medicines, other herbal products such as cosmetics, fragrances, teas, health foods, and nutraceuticals are equally popular and constitute a large proportion of global herbal business.

1.2 Historical practices

Historical practices determine the way herbal medicines are formulated and used. During the past two decades, there has been an increasing interest in the industrialized nations to use medicinal plants. Sources of details are pharmacopoeias, indigenous knowledge, scientific literature, and other documented sources.

Herbal medicine use is based on historical medicinal practices. In some cases (e.g., China), there are well-defined procedures that are well documented in pharmacopoeias dating back nearly 2000 years and other monographs. However, this is not always the case, and in a number of countries the knowledge base is constantly being eroded. Indigenous people generally state that herbal medicines must be prepared in the traditional way to be described as herbal medicine. The ongoing need to catalogue actual uses of medicinal plants continues.

Several well-known medicines are derived from plants. These include morphine, digitoxin, taxol, colchicine, and L-hyoscyamine.

The plant processing encompasses drying, mechanical disruption, and solvent extraction (aqueous or organic solvent, e.g., ethanol), and will influence the final quality of the herbal product. Analytical procedures can be used to determine the active constituents that are present in herbal substances. Standardized extracts are prepared with ethanol and may be referred to as phytomedicines. Differences in levels of active constituents in herbal substances may be dependent on both locality of collection and annual growth cycles of the source herbs.

Herbal products are defined as herbal materials that are administered to patients and are mixtures of herbal substances and other constituents [6]. The importance of herbal medicine practices is indicated by the fact that about 80 % of the developing world's population depends on traditional medicine for their primary healthcare. The scientific evaluation of safety and efficacy of herbal products and medicinal preparation is thus of vital importance from both medicinal and economic perspectives.

Consideration of the growing importance of herbal medicine and other herbal preparations, concerns about the safety and claimed efficacy of many herbal products, and lack of proper scientific evaluation resulted in IUPAC supporting the current project with the objective of preparing protocols on safety, efficacy, standardization, and documentation of herbal medicine. These protocols are presented here. Further details of these topics will be published soon in a monograph.

2. SAFETY OF HERBAL MEDICINE

2.1 Introduction

Herbal medicines are generally regarded as safe based on their long-standing use in various cultures. However, there are case reports of serious adverse events after administration of herbal products. In a lot of cases, the toxicity has been traced to contaminants and adulteration. However, some of the plants used in herbal medicines can also be highly toxic. As a whole, herbal medicines can have a risk of adverse effects and drug—drug and drug—food interactions if not properly assessed.

Assessment of the safety of herbal products, therefore, is the first priority in herbal research. There are various approaches to the evaluation of safety of herbal medicines. The toxic effects of herbal preparation may be attributed mainly to the following:

- inherent toxicity of plant constituents and ingredients
- manufacturing malpractice and contamination

Evaluation of the toxic effects of plant constituents of herbal formulation requires detailed phytochemical and pharmacological studies. It is, however, safe to assume that, based on human experiences in various cultures, the use of toxic plant ingredients has already been largely eliminated and recent reports of toxicity could largely be due to misidentification and overdosing of certain constituents.

2.2 Contaminants in herbal medicine

Potential contaminants of herbal medicines include microorganisms, microbial toxins, pesticides, fumigation agents, radioactivity, and the presence of toxic compounds of toxic metals [7–10]. Some of these contaminants have been identified by the Committee for Proprietary Medicinal Products (CPMP) of the European Community (EC) for use in controlling the purity of herbal medications in the European Union (EU) [11]. The CPMP Guidelines highlight the need for good control of starting materials and the finished product and emphasize the importance of good manufacturing practice. Potential contaminants are listed in Table 1.

Table 1 Potential contaminants	s requiring	monitoring in	the q	uality	control	of
traditional Chinese medicines	[4].					

Type of contaminant	Examples
Microorganisms	Staphylococcus aureus, Escherichia coli (certain strains), Salmonella, Shigella, Pseudomonas aeruginosa
Microbial toxins	Bacterial endotoxins, aflatoxins
Pesticides	Chlorinated pesticides (e.g., DDT, dieldrin), organic phosphates, carbamate insecticides and herbicides, dithiocarbamate fungicides, triazin herbicides
Fumigation agents	Ethylene oxide, methyl bromide, phosphine
Radioactivity	Cs-134, Cs-137, Ru-103, I-131, Sr-90
Metals	Lead, cadmium, mercury, arsenic

Contamination other than with toxic metals in Chinese herbal preparations has not been reported in the literature. Apparently, these other contaminants have not been the focus of any extensive investigation so far. Reports of toxic metal contamination include lead, arsenic, mercury, thallium, and cad-

mium poisoning [10-14]. Table 2 lists the toxic metal contaminants identified in Chinese herbal remedies.

Chinese herbal products	Toxic metals found	Adverse effect
An gong niu huang wan, da huo luo wan, niu huang chiang ya wan, niu huang ching hsin wan, tsai tsao wan, <i>Dendrobium moniliforme</i> Nightsight pills	Arsenic, mercury	Associated toxicity
Bal jivan chamcho (Asian)	Lead	Lead toxicity
Surna (Asian)	Lead	Lead toxicity
Nutrien	Thallium	Alopecia

Table 2 Identified contamination of Chinese herbal medicines with toxic metals.

Numerous reports exist in the literature indicating that certain herbal medicines, in particular TCMs, may contain high levels of arsenic and heavy metals [9,15–16]. For example, out of a total of 251 products, 24 contained lead (10–319 mg/kg), 36 contained arsenic (20–140 000 mg/kg), and 35 contained mercury (22–5070 mg/kg) [16].

2.2.1 Substitution and misidentification of herbal substances

Risks associated with herbal medicine products were first reported for medicinal plants of the Asteraceae family, *Hypericin* and *Aristolochia* genus, and kava-kava. A number of cases of inadvertent or deliberate substitution of the constituents of Chinese herbal preparations are cited in the literature. For example, Siberian ginseng (*Eleutherococcus senticosus*), American ginseng (*Panax quinque-folium*), and Japanese ginseng (*Panax pseudo-ginseng*) have been substituted for Korean or Chinese ginseng (*Panax ginseng*). Sometimes the substitute has a much greater toxicity than the original material. Examples of substitution resulting in an adverse effect include reported cases of hepatitis with jin bu huan [17], renal fibrosis due to *Aristolochia fangchi* [18], and podophyllin poisoning due to *Podophyllum emodi* [19]. Table 3 lists reported substitutions in Chinese herbal medicines. Acute hepatitis by a Chinese herb shou-wu-pian, mainly containing *Polygonum multriflorum*, has also been reported [20].

Cases of hepatitis related to consumption of jin bu huan (*Lycopodium serratum*) were reported in seven patients in the United States. Jin bu huan is used for pain relief and insomnia [17]. The reaction developed after an average of 20 weeks of therapy and was resolved in most patients in a mean of 8 weeks. The information enclosed with the preparation indicated that the product contained 30 % levoalkaloid from *Polygala chinensis*, but analysis suggested a more toxic substitute [21,22], an alkaloid from *Stephania* and *Corydalis* genera and not from *Polygala* [17].

A number of cases of interstitial renal fibrosis caused by presence of aristolochic acid have occurred. More than 70 cases of renal failure following ingestion of a slimming preparation containing Chinese herbs were identified in Belgium [23,27] between January 1989 and January 1994. Of these, 30 progressed to terminal renal failure [23]. Nephropathy was characterized by extensive interstitial fibrosis with atrophy and loss of the tubules [24,25]. There was also the suspicion of increased renal malignancies in these patients [28].

The preparation was known to contain *Stephania tetrandra* and *Magnolia officinalis*, but initial investigations suspected substitution of *Aristolochia fangchi* for *S. tetrandra* due to possible mistakes in nomenclature. *Aristolochia* spp. contain aristolochic acid, which is nephrotoxic in animals and humans [26]. Incidentally, features of Balkan endemic nephropathy, a severe renal side effect in which aristolochic acid has been suggested as a possible cause, are similar to those reported in Belgium [28].

The initial reports failed to detect the presence of aristolochic acid [19], but more sophisticated investigations suggested that particular batch of herbs labeled *S. tetrandra* contained aristolochic acid and not tetrandrine [28].

Reported ingredient	Substituted ingredient(s)	Possible reason	Resultant toxicity	References
Long dan cao Gentiana spp.	Gui jiu (Podophyllum emodi)	Similarity in appearance or difficulty with nomenclature	Podophyllin poisoning	[12,19]
Korean/Chinese ginseng (Panax ginseng)	Siberian ginseng (Elutherococcus senticosus), American ginseng (P. Quinquefolium)	Cost	N/A screening	[19]
Jin bu huan (Polygala chinesis)	Stephania corydalis	Poor practice	Hepatitis	[17,20]
Fang-jig Stephanie tetramer	Aristolochia fangchi	Similarity in nomenclature	Renal fibrosis	[18,22–24]
Ginseng	Rauwolfia serpentina	Cost	Not reported	[10]

Table 3 Substitutions observed with Chinese herbal medicine.

In Australia in 1999, the drug regulatory body, Therapeutic Goods Administration (TGA), reported two cases of misidentification of *Aristolochia* species for *Clematis* species, used by Australian manufacturers who provided samples for a voluntary audit of the products following a UK report of two new cases of end-stage renal failure associated with *Aristolochia* in Chinese herbal medicines [29].

Madragora officinarum

There are numerous reports of inadvertent substitution of "gui jiu" (*Podophyllum emodi* Wall) for "long dan cao" (*Gentiana* spp.) [19]. This resulted in severe neurological, gastrointestinal, renal, and hepatic manifestations in the consumers [19].

Herbal medicines are largely unregulated as drugs, and contamination is an important issue with their use. Herbal medicines are popular in developing countries as they are generally linked to traditional practices and available plant sources. Consequently, herbal medicines have an important role in primary healthcare in these countries.

The legal situation regarding herbal preparations varies from country to country. Herbal products range from phytomedicines to food and dietary supplements where therapeutic claims are not allowed. There may be a strong connection with traditionally used herbal medicines and folkloric knowledge, which in some countries justifies less stringent regulations. Generally, there are no universal legislative criteria for use in regulating herbal products.

2.2.2 Documented or regulatory approaches

Herbal medicines were first included in the WHO International Conference on Drug Regulatory Authorities in 1986 [30]. In 1991, WHO prepared draft guidelines for assessment of herbal medicines, which were adopted by the 6th International Conference on Drug Regulatory Authorities (ICDRA) [31]. This includes basic criteria for quality, safety, and efficacy of herbal medicines. These guidelines provide valuable assistance to national regulatory authorities, scientific organizations, and manufacturers to undertake assessment of documentation of submissions.

Following the recommendations of the 6th ICDRA in 1991, WHO continued to develop pharmaceutical monographs on herbal medicines on the basis of guidelines for the assessment of herbal medicines

icines [32,33]: Part I: Botanical Characteristics, Major Active Constituents, and Quality Control (QC); and Part II: Summaries of Clinical Applications, Pharmacology, Precautions, and Adverse Reactions.

The purpose of the WHO monographs was to

- provide scientific information on safety, efficacy, and quality control of medicinal plants; and
- facilitate proper use of herbal medicines.

In the United States, herbal products can only be marketed as food supplements. Specific health claims need U.S. Food and Drug Administration (FDA) approval. The *European Guidelines for the Assessment of Herbal Medicines* state that a substance's historical use is valid to document safety and efficacy, in the absence of scientific evidence to the contrary.

Two features of the European approach are as follows:

- Costs are less, it takes less time to approve herbal medicines as safe and effective, and one can apply the "doctrine of reasonable certainty", which does not compromise safety.
- No inherent prejudice exists against complex plant substances; they are considered safe and effective.

The EC has a complex legislative framework that allows for the use of herbal medicines. Directive 91/507/EEC gives details of quality, safety, and efficacy. Further directives followed, e.g., European Directive 2004/24/EC of 31 March 2004. Similarly, the United Kingdom has adopted a Statutory Instrument No. 2750 entitled "The Medicines (Traditional Herbal Medicinal Products for Human Use) Regulations 2005".

The European Scientific Cooperative on Phytotherapy (ESCOP), founded in 1989, has produced a number of comprehensive monographs. ESCOP and WHO monographs are used in many member states as summaries and sources of bibliographic data.

The use of herbal medicines is commonplace in Germany. As a consequence, the German Federal Health Agency Commission E was formed in 1978 to evaluate the safety and efficacy of 380 herbal medicines. Its monographs contain pharmacological, toxicological, and clinical documentation. Developments in other countries have been summarized [34].

Requirements for pharmaceutical assessment that cover the safety assessment of herbal products are as follows:

- experience of safety
- toxicological studies, where vindicated

The risks associated with the use of herbal substances, which has unfortunately resulted in a number of fatalities, are considered highly significant and are related to problems associated with the failure of good handling and manufacturing of certain products. Lack of standardization, contamination with toxic metals, inadvertent and deliberate substitution of other herbs, and adulteration with Western pharmaceuticals also contribute in associated risks. Clearly, there is a danger to the public without a proper evaluation of the possible risks which could arise from the ingestion of medicinal herbs.

2.2.3 Development of monitoring and surveillance systems

Herbal medicinal products are classified as a drug without a therapeutic claim in many countries. A therapeutic claim means classification as a drug product and subject to drug regulations as followed in some developing countries. For the application of general health laws to herbal products, microbiological tests are used as a means to assess safety. For standardization, safety, and efficacy assessment, legislation must be introduced to ensure that required standards are met. It is therefore necessary to keep pace with changing consumer needs. New approaches such as supercritical fluid extraction (SPE) can substantially improve purity of extracts of plant materials. Serious herb—drug interactions are rare, and trials are unlikely to detect most cases. Quality assurance is, therefore, of paramount importance.

What is needed is a balance between industry and regulation in order to protect public health. The practice developed for herbal medicines through the Joint Agency Model–Joint Tasman Project [35], used a risk-based approach as follows:

- by substance
- by claim

The TGA [31] approach was sound, but its risk application was poor. The evaluation of new herbal products consists of six steps, which define the following:

- characteristics of new substances,
- history and pattern of use,
- any adverse reaction,
- biological action,
- · toxicity and carcinogenicity, and
- clinical trial data.

The presence of impurities is either

- an intended addition, or
- accidental contamination via processing.

The substitution of plants arises because of

- similar plants/wrong identification, or
- the use of cheaper alternatives.

2.2.4 Assessment of toxicity

For herbal products, analysis of the active pharmaceutical ingredients may be best approached by analysis of one or more hypothesized active ingredients, analysis of a chemical constituent that constitutes a sizeable percentage of total ingredients, and chemical fingerprinting of ingredients [36]. Toxicity investigation will also be required because the analysis alone is unlikely to reveal the contributions to toxicity itself. In assessing toxicity of an herbal medicine, the dose chosen is very important.

Toxicity assessment involves one or more of the following techniques:

- in vivo techniques
- in vitro techniques
- cell line techniques
- micro-array and other modern techniques
- standardization
- techniques to adequately model toxicity

The issues of mixtures and deviation from conventional pharmacological approaches remain a major problem, along with the consequences of using the wrong source plants or ingredients, variable content of active constituents, and a narrow therapeutic window with herbal medicines. Concurrent contamination with any one of the toxic metals, bacteria, viruses, or pesticides may also occur.

2.2.5 Risk assessment approach

The risk assessment procedure considers the following steps in risk characterization:

- hazard identification
- dose–response assessment
- exposure assessment

Risk characterization enables the estimation of any adverse effect and provides a means of devising risk management, if appropriate. Risk management can then be applied on the basis of the assessments given below:

Risk assessment is a process that enables management and communication tools to be developed to control any adverse effects of pesticide applications during cultivation and storage of medicinal herbs [37]. It comprises the discrete steps of identification of source and hazard, dose response, exposure, and calculation of risk [38]. There are acceptable risk management concepts which can be applied to public health and the environment, arising from exposure to pesticides. There are two groups at risk [39], namely, (i) workers handling herbal products, and (ii) people using herbal products.

In the risk assessment process, studies need to take into account formulation of the herbal products and their bioavailabilities. It is necessary to combine quality application data with chronic toxicity data. However, these are rarely available for most herbal products.

Currently accepted procedures in Australia [40] and by the USEPA [41] enable the formalized approach of risk assessment to be applied when required. Calculation of dose enables recommendations to be made regarding safety criteria for public health. The understanding of risk assessment and implementation and management are two sequential steps where assessment is first undertaken followed by development of a management tool based on identified risks. In many cases, a complete risk assessment may not be undertaken for practical reasons. In such cases, decision-making tools are developed to provide a risk-based approach that acts as a framework.

The outcome of the risk assessment process is, therefore, to determine whether risk characterization identifies any significant aspect of the toxicant(s) in any particular herbal product.

2.2.5 Challenges

A key challenge is to objectively assess conflicting toxicological, epidemiological, and other data and the verification of herbal materials used. This requires use of the audit process to identify potential contaminants in herbal products. The following key issues remain.

- management within ranges of risk
- communication of uncertainty
- pharmacovigilance
- · understanding why addition of harmful additives works
- evaluating "drug" interactions
- constraints with clinical trials and people available

3. EFFICACY OF HERBAL MEDICINE

3.1 Introduction

The efficacy of medicine is the measure of its ability to improve health and well-being. This is a central issue in the modern debate about herbal medicine. The use of herbal remedies is often justified by their long history of usage—from prehistoric time in some cases. But, age-old wisdom does not necessarily guarantee that the product in question is efficacious with reasonable specificity. The term "efficacious", however, has a relative meaning as it may be interpreted differently by the practitioners of traditional medicine (of which herbal medicine is a type) and the proponents of so-called modern medicine (conventional medicine). Traditional medicine usually takes a "holistic" approach where the physical, spiritual (which includes mental), and most often social well-being of an individual are treated. Thus, the medicinal value of an herbal product may be intimately related to its nutritional and psychological aspects. Although this philosophy is not consciously followed by many traditional practitioners nowadays, it remains a natural corollary of their system that the efficacy of their intervention cannot simply be judged by physiological and biochemical indicators. Modern medicines, on the other hand, are relatively more focused on particular diseases based on specific etiopathological entities. WHO has defined

health in terms of both physical and mental well-being. However, modern medical practice usually emphasizes only physical well-being. In recent times, the trend in the right direction is to develop more of an integrated approach of treatment involving physical, mental, and social well-being.

One way to bridge the philosophical gap between these two systems (and thus to adopt more of an integrated approach) is the WHO concept of health, which emphasizes the best part of both systems. Through this "one system of medicine" we may be able to design appropriate indicators of efficacy and the practical methodology to test them. This will, however, require openness and understanding from both sides.

3.2 Assessment of efficacy

Herbal medicines are inherently different from conventional pharmacological treatments, but presently there is no way to assess their efficacy other than by currently used conventional clinical trial methodologies, in which efficacy is conventionally assessed by clinical, laboratory, or diagnostic outcomes:

- Clinical outcomes include parameters such as improved morbidity and mortality, reduced pain or discomfort, improved appetite and weight gain, reduction of blood pressure, reduction of tumor size or extent, and improved quality of life.
- Laboratory/other diagnostic outcomes include parameters such as reduction of blood glucose, improvement of hemoglobin status, reduction of opacity as measured by radiological or imaging techniques, and improvement in electrocardiogram (ECG) findings.

One of the crucial questions is whether these two groups of efficacy measures are sufficient for assessing the efficacy of herbal medicines. In particular, it is argued that socioeconomic, cultural, and psychological variables should be integrated with the clinical and diagnostic parameters in assessing the efficacy of herbal medicine. Socioeconomic variables are major issues also in modern medicine, but in this system these are normally separated from the biological outcome and integration is discussed only at the level of health system analysis, not at the efficacy level. Given the fact that most of the users of herbal medicine in developing countries have limited accessibility to and affordability for modern medicine, it would be natural to agree in favor of a greater emphasis on socioeconomic variables in this system of medicine. While this approach is attractive from a social and political point of view, it is still difficult to incorporate it into the practical assessment of efficacy of a particular herbal medicine. There is, however, scope to utilize the flexibility inherent in the modern scientific method for conducting studies on herbal medicines.

3.2.1 Methodology and tools for assessment of efficacy

As far back as the 4th century BCE, Aristotle in his famous book *Organon* defined the essence of scientific knowledge [42]. According to him, to create scientific knowledge, it is important to critically observe an event as well as study its cause. Thus, in medicine, it is not only sufficient to show that an intervention works, it is also essential to explain how it works. Science starts with observation, but that alone does not make science. The same rules apply for herbal products and conventional therapies. Although the desired or expected health outcomes of different treatments will vary, how evidence of the effectiveness of each treatment is gathered is basically the same. The design of a study determines the strength of the evidence, subject selection, randomization, mode of treatment, controlling, confounding variables, and reporting of results [43]. Usually the following tools are applied for testing the efficacy of drugs: (a) anecdotal reports, (b) case reports, (c) case series, and (d) randomized clinical trials [44].

Anecdotal reports are usually not taken into account in conventional medicine, but they are important components of the efficacy assessment in herbal medicine. This is due to the fact that lots of herbs have remained unexplored and that knowledge about their usefulness is often limited to individual practitioners or tribes, sometimes, living in isolated communities or peripheral locations. There should be an immediate concerted effort to collect these anecdotal reports as much

- of this knowledge is disappearing with time. Organization of these anecdotal reports into well-designed case series may provide useful data on the efficacy of a large group of herbal agents.
- Case reports are the starting point for efficacy (or toxicity) tests of many drugs, as evident from the contents of many reputable clinical journals. In one systematic review, they account for over one-third of all articles published in medical journals [45]. These can represent the first clues in the identification of new diseases, new interventions, or previously unknown adverse effects. Case reports can be retrospective (data collected from previous experiences or records) or prospective (follow-up from a baseline) in nature. The latter may again be divided into observational (collection of data by passive observation) or interventional (adjusting the system by standardized design) in nature.
- Case series are collections of individual case reports, organized to explore a particular association. The collection of a case series, rather than relying on a single case report, can mean the difference between formulating a useful hypothesis or merely documenting an interacting medical oddity. Case series may be retrospective or prospective (observational or interventional) in nature, as explained in case reports.
- Randomized clinical trials (with double-blind ones being the gold standard) are the ultimate
 measure of efficacy in conventional medicine. Substantial efforts and resources are necessary for
 such trials.

3.2.2 Application of conventional tools for testing efficacy of herbal medicine

As for conventional concepts, case reports and case series are very useful for hypothesis formulation, but they cannot be used to test the presence of a valid statistical association. One fundamental limitation of a case report is that it is based on the experience of only one person. The presence of any effect, however suggestive, may simply be coincidental. Although case series are frequently sufficiently large to permit quantification of the effect, the ability to interpret such information is severely limited by the lack of an appropriate comparison group. This lack can either obscure an effect or suggest an effect where none actually exists. Randomized clinical trials take away many of these biases and limitations that are present in the case series design.

Although randomized clinical trials should be the ideal way for evaluating the efficacy of herbal drugs, it cannot always be implemented for several reasons [46,47]. These trials are inherently interventional in nature, and it may be sometimes ethically questionable whether such studies can be designed without sufficient existing evidence about its efficacy and safety in animals. For edible plants or for plants used as herbal medicines since early times by human beings (pharmacopoeal), there may be an argument for conducting trials without animal experimentation, but there still remain unsolved ethical issues in this area.

Numerous variables (including sociocultural factors, beliefs, and placebo effects) influencing the effectiveness and quality of herbal drugs also make it difficult to design trials on these drugs. Use of conventional protocols for chemical analysis, animal experimentation, and toxicity studies blur the demarcation between traditional and modern pharmaceutical approaches. Moreover, there is a risk that the economic consequences of such an approach could offset the low-cost healthcare benefit currently enjoyed by the majority of the population who are most dependent on herbal drugs.

In the context of difficulties with randomized clinical trials, an increased scoring can be given to case report approaches in assessing the efficacy of herbal medicines. Retrospective observational data would be difficult to be compiled due to the lack of proper record systems in the case of individual or institutional traditional practitioners. It may, however, be possible to conduct qualitative studies on agelong practices, and the inferences may be used to strengthen the evidence for efficacy. Maximum emphasis should be given to organized studies with an internationally accepted design.

Prospective observational design will be the easiest to implement as a substantial amount of data from a large number of subjects, prescribed with herbal drugs under the existing legislations of a par-

ticular country, can be brought into a proper record system and analyzed scientifically. Lack of standardization in such cases, however, would pose considerable limitations on drawing any inferences.

Implementation of a standardized approach for the herbal practitioners and collection of the prospective data necessarily creates an interventional design which, if planned properly, may closely resemble single-blind randomized trials. Even if it differs from double-blind randomized trials in the degree of rigor, this design may be the optimum, both biologically and economically, for rapid evaluation of herbal products. Standardization, however, may sometimes be incompatible with the existing legislative framework and caution is needed regarding the ethical implications of such studies.

Although randomized clinical trials (with double-blind trials as the gold standard) are relatively difficult to be implemented in the case of herbal medicine, they are not ruled out per se in assessing the efficacy of these products. Data from case series studies may provide sufficient scientific and ethical validity to conduct such trials, but acceptance of this protocol needs a paradigm change in the methodology of drug evaluation as understood in conventional medicine.

Even with all the above-cited limitations, a large number of randomized clinical trials on herbal medicines have been successfully conducted and published. Two case studies are presented in boxes as examples.

Case I

Garlic (*Allium sativum* L.) is known to have multifold properties such as lowering of total serum cholesterol levels, anti-platelet activation, and anti-bacterial, -hypertensive, and -thrombiotic activities. There are numerous products of garlic available on the market.

Rigorous clinical trials have been conducted on garlic preparations, mainly for lipid-lowering properties. The outcome of these trials has been largely supportive of its regular use to prevent cardiovascular diseases. Epidemiological data indicate a protective effect of garlic against arteriosclerosis and various forms of malignancies.

Case II

Gingko (*Gingko biloba* L.) is among the most popular medicinal herbs of the world. Double-blind clinical studies on gingko preparations indicate a significant but modest increase in pain-free walking distance as compared to the placebo. Clinical studies also suggest that it can delay the clinical deterioration in dementia patients.

3.2.3 Toward a unified medicine

The sociocultural and philosophical issues which complicate the study of herbal medicine may be practically used if they can be integrated into our clinical practice. This is based on an understanding that health is not only a medical issue but a socioeconomic and cultural issue as well. The people practicing and promoting conventional medicine also need to understand that a drug does not necessarily have to be a pure compound. If drugs are defined as "effective interventional materials", then it is easier to find a common meeting point for the different systems of medicine. If the principles for assessing efficacy can be made flexible within the limits of scientific methodology, then herbal medicine can be an example for creating a consensus among the various systems.

3.2.4 Protocol for testing the efficacy of an herbal drug

The following is a recommended protocol for the evaluation of efficacy of herbal formulations.

STEP 1: EVALUATE THE PRIMARY SOURCE OF INFORMATION

1a. Anecdotal reports of users	Double-check the reports, if necessary by personal visits. Try to ascertain the nature of symptoms and signs (and investigation results whenever available) and make an assessment about the diagnosis of the disease, effect of the herbal drug, and potential confounders.
1b. Clinical experience of traditional healers	The evaluator should meet with a few healers personally and try to find out the common points regarding the signs and symptoms of the disease against which the herb acts. Also note the preparation and dispensing practices used by the different healers. Confounding variables must be noted.
1c. Clinical experience of modern practitioners	In addition to exploring the points mentioned in the case of traditional healers, make an effort to obtain their views on the clinical effect and possible target of the herb. You may acquire valuable investigation data from these cases. In the case of commercial preparations, consult the company, in order to identify the practitioners prescribing their product.
1d. Published works	Refer to multiple databases. Do not restrict searches to only medical and chemical databases, but also refer to agricultural, anthropological, or even sociological sources. Compile information and make your own database on the particular herb in question. Look for information on the chemical nature and clinical effects including the mechanism of action.

Link with Step 1



STEP 2: CREATE A HYPOTHESIS

Create your hypothesis using the evaluation of data from your primary sources. The hypothesis should have three parts (although they are not mutually exclusive):

- The drug is effective.
- The drug has x(y...) mechanism(s) of action.
- The drug is reasonably safe.

STEP 3: PLAN YOUR STUDIES ON EFFICACY AND SAFETY

Studies can be planned in the forms of

- case study
- case series
- animal experiments
- in vitro experiments
- uncontrolled clinical trial
- controlled clinical trial

Link with Step 1a

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3a. Case study

Organize new case reports based on the experience of the healers/modern practitioners and unpublished or locally published or internationally published reports. Carefully design your input and outcome variables, using modern laboratory/imaging investigations, as much as practicable. If you are a clinician, you can plan your own study, but in many cases you may prefer to involve a practitioner who is already using herbal medicine.

Link with Steps 1b and 1c



3b. Case series

Organize a group of practitioners and institutes who regularly prescribe the herbal medicine. Develop a study protocol with specific input and outcome variables, laboratory/imaging investigations, and statistical tools. It is difficult to plan homogeneous practices, but one should create a consensus as far as possible before starting the investigation.

Link with Steps 1a-1d



3c. Uncontrolled clinical trial

This is probably the most practical option for testing the efficacy of an herbal medicine. Organize a single center or multicenter study with a stringent protocol both from the chemical and biological sides. Use the same agent prepared from the same lot of plant materials and standardize the route of administration, dose, time of administration, confounding drugs or diet, lifestyle recommendations, and all other potential issues which may affect the outcome.

Link with Steps 1a-1d



Standardize the input variables

From the chemical side:

- species of the plant (identified by a plant taxonomist)
- physical processing
- chemical methods of preparation
- chemical analysis or fingerprinting, if possible
- preservation and storage
- stability studies (analyze for consistency at set intervals)—see fourth point
- dispensing techniques
- dosage, timing, relation with food
- use of adjuncts
- advice on diet
- advice on lifestyle, particularly exercise

From the biological side:

- identification of subjects using well-defined clinical variables in terms of signs, symptoms, investigation results, and diagnosis
- measurement of anthropometric and socioeconomic variables, which may potentially influence the outcome of the treatment

Link with Step 2



Standardize the outcome parameters

This is a crucial issue. The variables should be defined according to the resources and facilities available, but a minimum level must be maintained (if necessary, by collaboration) to give scientific validity to the study. Outcome variables will include:

- anthropometric and clinical results
- investigation results (laboratory, imaging, electrophysiology, etc.)
- psychosocial and cultural results

The last group of variables needs to be specially mentioned in herbal medicine research. Frequently, the use of traditional medicine is linked with certain beliefs, practices, and other anthropological issues which may have physical and psychological impact with consequent effect on the outcome.

In many cases, these are also part of religious beliefs. Moreover, economic issues are an intimate part of these beliefs and practices. It is therefore important to carefully enumerate some variables in this area to have a comprehensive evaluation of the product.

Link with Step 3C

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3d. Controlled clinical trials

Decide carefully whether a double-blind clinical trial is at all feasible with the product in question.

For scientific validity, a double-blind controlled trial is preferable, not mandatory (see main article). Conduct a single-blind clinical trial whenever feasible.

For both types of trials, the methodology and statistical designs are similar to those used for pharmaceutical products. There are, however, some points for herbal medicine which should be specially noted.

In brief, generalization about the efficacy of herbal medicines is often not possible. Each herbal formulation needs to be assessed based on its merit. Most herbal medicines by far have not been subjected to extensive clinical testing.

4. STANDARDIZATION OF HERBAL MEDICINE

4.1 Introduction

Traditional medicine implies knowledge and practice of herbal healing for the prevention, diagnosis, and elimination of physical, mental, or social imbalance [48]. The costs for health care are rising at an alarming rate throughout the world. At the same time, the world market for phytopharmaceuticals is growing steadily. The World Bank estimates that trade in medicinal plants, botanical drug products, and raw materials is growing at an annual rate of between 5 and 15 % [49–51].

The proportion of plant-derived drugs differs from country to country. For example, while approximately 25 % of prescriptions in the United States contained plant-derived active ingredients, 40 % of the drugs on the German list of medicines ("Rote List") were based on plant material [52]. In some countries such as Malaysia, the plant origins of routinely prescribed medicines are easily assessed and well documented. Herbs, used as medicine, are also regulated under different categories throughout the world. Institutionally prepared formulas are often readily available without prescription. In some European countries, standardized concentrated extracts are regulated as drugs which can be obtained by prescription only. Herbs are considered to be dietary supplements in the United States and therefore are subjected to a very limited form of regulation and oversight [53].

It is a common observation that people diagnosed with incurable chronic disease states such as diabetes, arthritis, and AIDS turned to herbal therapies for a sense of control and mental comfort from taking action [54]. Herbal product studies cannot be considered scientifically valid if the product tested has not been authenticated and characterized in order to ensure reproducibility in the manufacturing of the product in question. Several studies have indicated quantitative variations in marker constituents in herbal preparations. Moreover, many dangerous and lethal side effects have recently been reported, including direct toxic effects, allergic reactions, effects from contaminants, and interactions with drugs and other herbs. Of the 10 most commonly used herbs in the United States, systematic reviews have concluded that only 4 are likely to be effective and there is very limited evidence to evaluate the efficacy of the approximately 20 000 other available herbal products [55].

Case III

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 content 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. Eleutherosides B and E content of Eleuthero coccus root powder and other formulated extract products also showed a large variation. 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 by using an official U.S. Pharmacopoeia (USP) spectrophotometric procedure and from 47 to 165 % when analyzed by high-performance liquid chromatography (HPLC) method [56]. Furthermore, nephropathy or end-stage renal failure was reported in patients taking weight-reducing pills containing Chinese herbs. This happened because of a manufacturing error when one of the medicinal plants in the pills was replaced with Aristolochia fangchi, which contains aristolochic acids as its main components [57]. The presence of undeclared drugs, such as chlorphenamine, paracetamol, and others, can be found in health supplements and herbal preparations, as has been reported in some countries [58].

Recent surveys reported in the American news media indicated that a large percentage of the public would like to see products supported by science, which means products supported by clinical research. This means consumers are increasingly demanding products of known quality. This is where the public standards enter into the picture [59]. There is a strong demand and need to accelerate the research in phytomedicine [60].

Standardized herbal products of consistent quality and containing well-defined constituents are required for reliable clinical trials and to provide consistent beneficial therapeutic effects. Pharmacological properties of an herbal formulation depend on phytochemical constituents present therein. Development of authentic analytical methods which can reliably profile the phytochemical composition, including quantitative analyses of marker/bioactive compounds and other major constituents, is a major challenge to scientists. Without consistent quality of a phytochemical mixture, a consistent pharmacological effect is not expected. Resurgence of interest and the growing market of herbal medicinal products necessitate strong commitment by the stakeholders to safeguard the consumer and the industry. Standardization is the first step for the establishment of a consistent biological activity, a consistent chemical profile, or simply a quality assurance program for production and manufacturing. Therefore, the EU has defined three categories of herbal products:

- those containing constituents (single compounds or families of compounds) with known and experienced therapeutic activity that are deemed solely responsible for clinical efficacy;
- those containing chemically defined constituents possessing relevant pharmacological properties which are likely to contribute to the clinical efficacy; and
- those in which no constituents have been identified as being responsible for the therapeutic activity.

Standardization as defined in the text for guidance on the quality of herbal medicinal products means adjusting the herbal drug preparation to a defined content of a constituent or group of substances with known therapeutic activity. The European Medicines Agency (EMEA) makes the distinction between constituents with known therapeutic activity which can be used to standardize a biological effect and

marker compounds which allow standardization on a set amount of the chosen compound. The EMEA defines marker compounds as chemically defined constituents of a herbal drug which are of interest for control purposes, independent of whether they have any therapeutic activity or not. Examples of markers are the valerenic acids in *Valeriana officinalis* L., gingkolides and flavonoids in *Ginkgo biloba* L., and hypericin and hyperforin in *Hypericum perfoliatum* L. [61–63].

4.2 Current status

Herbs are generally defined as any form of a plant or plant product, including leaves, stems, flowers, roots, and seeds [64]. Herbal products may contain a single herb or combinations of several different herbs that are believed to have complementary effects. Some herbal products, including those of TCM formulations, also include animal products and minerals [65]. Herbal products are sold as either raw plants or extracts of portions of the plant. The extraction involves boiling, percolating, or macerating the herb in water, ethanol, or other solvents to release biologically active constituents from the cell matrices of the plant into the solvents. The herb to be extracted may be in its dried or fresh forms.

Regulatory requirements for the quality of herbal products vary depending on the country and the regulatory category. The same herbal product can be marketed as a drug in Europe and as a dietary supplement in the United States. In Europe, medicinal plant products are produced according to quality standards typical for pharmaceutical products. This is especially true for potent herbal products in which the active ingredients are defined, contribute substantially to the therapeutic activity, and allow standardization of a constituent(s) within a set range supported by a pharmacopoeial monograph. Individual governments, the WHO, and panels of academic experts and clinicians often provide guidelines for manufacturing and quality control, as well as therapeutic use in terms of indication, dose, side effects, and possible safety concerns. Many of these guidelines are compiled in pharmacopoeial monographs. These guidelines are governed by regulations that cover all aspects from manufacturing to labeling and advertising of the finished products. In the United States, compliance of dietary supplements to a pharmacopoieal monograph is optional. Thus, it is difficult for consumers of dietary supplements to make informed decisions about self-medication based upon label information. The level of quality control employed by different manufacturers varies widely. Claims of standardization are made without definition of the term or indication of whether the chemicals used in standardization are responsible for therapeutic effect. Without all this information, the consumers can make purchasing decisions based upon price only.

The most established information with regard to the use of herbal preparations currently available in the public domain is in the form of pharmacopoeial monographs. These documents publish traditional and standardized therapeutic uses of herbs and provide a foundation for clinical practice. Monographs consist of a description of the herb, including botanical information, laboratory analysis, therapeutic indications, and drug interactions (if relevant). Although the monographs may be tedious to read, they include specific information that may not be available in other references. Several national and international organizations have adopted the monograph format. Some examples are given in the box below.

Examples of Monographs

- American Herbal Pharmacopoeia: 4 monographs (type: standards, therapeutic; includes Chinese and Ayurvedic herbs).
- *British Herbal Pharmacopoeia*: 169 monographs (type: standards; referenced, revised in 1996)
- *British Herbal Compendium*: 84 monographs corresponding to 84 herbs listed in 1990 edition of BHP (type: therapeutic; referenced)
- European Scientific Cooperation for Phytotherapy (ESCOP): 50 herbal monographs (type: therapeutic; referenced)
- German Commission E (ABC translation): 433 monographs (including revisions), 324 herb and combinations, 200 approved herb (type: therapeutic; no longer being evaluated and produced by German government; not referenced) [66].
- *United States Pharmacopoeia*: 11 monographs (type: standards (8), therapeutic (3); therapeutic monographs)
- World Health Organization: 28 monographs covering 31 plant species (type: standards, therapeutic)

According to the draft guidelines of FDA [67] and the European Agency for the Evaluation of Medicinal Products [68], various aspects of analysis as recommended in respective pharmacopoeias, must be performed for the purpose of certification of botanical drugs and herbal preparations. For herbal preparations, in addition to the tests mentioned, the results of other tests, including disintegration, dissolution, and hardness/friability and uniformity of dosage unit, should also be made available. Clinical studies may be initiated at phase II for common botanicals. The continuing efforts to optimize health in today's society has created a huge market for dietary supplements, further highlighting the growing need to validate methods of analysis in botanicals and herbal preparations.

The most important step in the development of analytical methods for botanicals and herbal preparations is sample preparation. The basic operation includes steps such as pre-washing, drying of plant materials, or freeze-drying and grinding, to obtain a homogenous sample and often improving the kinetics of extraction of the constituents. In the pharmacopoeial monographs, methods such as sonication, heating under reflux, Soxhlet extraction, and others are commonly used [69,70]. However, such methods can be time-consuming, require the use of a large amount of organic solvent, and may have lower extraction efficiencies. New methods are continuously being sought to address this issue. As target compounds may be polar or nonpolar and even thermally labile, the suitability of the methods of extraction must be considered. To reduce or eliminate the use of organic solvents and improve the extraction processes, newer sample preparation methods, such as microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), and accelerated solvent extraction (ASE) or pressurized liquid extraction (PLE) have been introduced for the extraction of targeted constituents present in plant materials.

Case IV

In MAE, microwave energy is used for heating the solution and results in significant reduction in extraction time (usually completed in less than 30 min). Other than having the advantage of high extraction speed, MAE also enables a significant reduction in the consumption of organic solvents [71–73]. The use of PLE on polar steroids, such as withanolides from the leaves of *Lochroma gesnerioides* and cocaine and benzylecgonine from coca leaves has been reported [74,75]. To reduce the use of organic solvent, pressurized hot water extraction (PHWE) has been used for the extraction of essential oil components from plant materials [76,77]. Subcritical water under pressure and between 125 and 175 °C had been used to rapidly extract oxygenated fragrance and flavor compounds from rosemary [78].

Separation of individual components from the herbal mixture is the key step to enable identification and bioactivity evaluation. Chromatography is a powerful analytical method suitable for the separation and quantitative determination of a considerable number of compounds, even from a complex matrix. These include paper chromatography (PC), thin-layer chromatography (TLC), gas chromatography (GC), HPLC, and capillary electrophoresis (CE). UV absorption has been the most commonly used detection method for the preliminary identification of the separated components. However, various other detectors, such as fluorescence (FD), flame ionization (FID), electron capture (ECD), refractive index (RI), and most recently, evaporative light scattering (ELSD), are also available for specific cases. Most of these detection methods allow the quantification of chemical compounds present in plant material or herbal product. The availability of high-speed computing and the appropriate software allows detection by using mass spectrometry (MS). This method not only allows the detection of component peaks of a mixture separated by chromatography but also in combination with UV (using a photodiode array detector), multistage MS and nuclear magnetic resonance spectrometry (LC–UV–MS–NMR), allows its molecular characterization [79,80].

More recently, NMR metabonomics, in combination with chemometrics, especially principal component analysis (PCA) and simulated independent modeling of class analogy (SIMCA) algorithms, has been recognized as a very powerful tool to classify samples according to their total chemical composition. The resolution of high-field NMR can provide information in the orders of magnitude higher than of other fingerprinting technologies such as usual NMR spectrometry or HPLC. This is a nonreductive fingerprinting method of the total chemical composition of samples [81–84].

The presence of toxic metals is also one of the parameters included in pharmacopoeias. The tool primarily used to detect and quantify the elements in most analyses is based on atomic absorption spectrometry (AAS). Currently, there have been a number of instruments developed based on the same principle, such as inductively coupled plasma—optical emission spectrometry (ICP—OES). Detection and quantification based on mass spectrometry has also been available using inductively coupled plasma—mass spectrometry (ICP—MS).

4.3 Protocols for standardization of herbal drugs

In order to assure a consistent and acceptable quality herbal product, care should be taken right from the identification and authentication of herbal raw materials to the verification process of final product. The following parameters are recommended.

1. Authentication	The first stage is identification of the plant species or botanical verification by the currently accepted Latin binomial name and synonyms [85]. The steps involved in authentication are taxonomic, and macroscopic and microscopic studies. Records should be maintained for stage of collection, parts of the plant collected, regional status, botanical identity such as phytomorphology, microscopial, and histological analysis, taxonomical identity, etc.
2. Physical parameters	Physical tests [86] include organoleptic evaluation (sensory characters such as taste, appearance, odor, feel of the drug, etc.), viscosity, moisture content, pH, disintegration time, friability, hardness, flowability, sedimentation, and ash value.
3. Chromatographic and spectroscopic evaluation	Sophisticated modern techniques of standardization such as UV–vis spectrophotometry, TLC, HPTLC [86,87], HPLC [88–91], NMR [92,93], near infrared spectroscopy [94] provide quantitative and semiquantitative information about the main active constituents or marker compounds present in the crude drug or herbal products. Markers play an important role in fingerprinting of herbs. Quality of drug can also be assessed by chromatographic fingerprint [95].
4. Microbiological parameters	Microbiological contamination can be measured according to methods described in the <i>Romanian Pharmacopoeia</i> [95], as well as in the <i>British Pharmacopoeia</i> [96]. Microbiological analysis includes analysis of limits of <i>E. coli</i> and molds, total viable aerobic count, total enteriobacteria and their count, aflatoxin analysis.
5. Pesticide residue analysis	Standard limits of pesticides have been set by WHO and FAO (Food and Agricultural Organization). Some common pesticides that cause harm to human beings, such as DDT, BHC, toxaphene, and aldrin, should be analyzed [97–100].
6. Heavy metal analysis	Toxic metals such as Cu, Zn, Mn, Fe, and particularly Cd, As, Pb and Hg should be analyzed [101–103]. In the analysis of metals, their speciation is to be taken into consideration.

4.4 Constraints and challenges

Both the raw herb and the extract contain complicated mixtures of organic chemicals which may include fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, lignans, and terpenes as well as other small molecules such as peptides and oligosaccharides. It is often difficult to determine which component, if any, of the herb has biological activity in humans. In addition, the processing of herbs, such as heating or boiling, may alter the dissolution rate, or even the pharmacological activity of the organic constituents. Similarly, a host of environmental factors, including soil, altitude, seasonal variation in temperature, atmospheric humidity, length of daylight, rainfall pattern, shade, dew, and frost conditions, may affect the levels of components in any given batch of an herb. Other factors, including

infections, insects, planting density, competition with other plant species, seeding time, and genetic factors, play an important role in producing uniform herbal products [104].

Plant collection for the use in botanicals is one of the factors of concern for quality. Plants collected in the wild may include nontargeted species, especially either by accidental substitution or intentional adulteration. Adulteration of herbal products can be made in various ways; commonly, adulteration is made by substituting other easily available, or cheap plant species or sometimes by spiking of a product with synthetic constituents.

An example of adulteration or willful substitution is the use of *Illicium anisatum* (Bastard anise), in place of *Illicium verum* (Star anise). *I. anisatum* contains the highly toxic anisatin which is regulated as one of the most powerful poisons of plant origin. As a consequence of its use, several adverse cases were reported from many countries in Europe [105].

In September 2003, the FDA advised consumers not to consume tea containing star anise. Such teas have been linked with serious neurological effects such as seizures, vomiting, jitteriness, and rapid eye movement. Some investigators had found Chinese star anise (*Illicium verum*) to be contaminated with the Japanese star anise (*Illicium anisatum*), which is a known neurotoxin. Chinese star anise was recognized as safe in food by the FDA, as acknowledged in the FDA's advisory. Chinese star anise was believed to help with colic in infants; however, the FDA was unaware of any scientific evidence to support this claim. In addition, the FDA has not identified the specific type of star anise associated with the adverse effects. Similar reports of adverse effects have been found in Florida, Illinois, New Jersey, and Washington in the United States as well as the Netherlands, Spain, and France.

Authenticated raw material is the basic requirement for the development of quality product. For authentication and quality, standardized products supported by good scientific research are the fundamental requirement. One of the challenges scientists face in this field is to develop validated methods to ensure quality control in botanicals from raw materials to finished products for optimal efficacy and safety of the products.

Detailed pharmacological experiments with single isolated compounds vs. the original extract or extract fractions have confirmed that many plant constituents, among them primarily phenolic compounds and terpenoids, exert "polyvalent pharmacological" effects [106]. This might explain some of the pharmacological synergistic effects and the phenomena observed, indicating that very often an extract possesses a much better therapeutic effect than single isolated constituents.

Case V

It was shown that hawthorn (*Crataegus oxyacantha*), which was indicated for the treatment of heart insufficiency grades I and II, possesses a positive inotropic activity, an ACE-inhibitory and vessel dilatative activity in angina pectoris. The active compounds of garlic (*Allium sativum*), ajoene and allicine, have a cholesterol- and lipid-lowering activity, act as antioxidants, inhibit NO formation and have an antihypertensive action. It was also shown that ajoene induces apoptosis in human leukemic cells, probably via the induction of reactive oxygen species. However, the clinical relevance has not yet been investigated [67–69]. These examples demonstrate that active compounds of a plant are able to act via different mechanisms of actions with relevance to entirely different diseases [106–108].

The role of the synergistic effects of more than one constituent present in herbal extracts has also been recognized in a number of studies.

Case VI

The efficacy of the root of *Urtica dioica* in prostate hyperplasia is probably based on a synergism of anti-proliferative and anti-inflammatory effects caused by lectins and polysaccharides. The leaves of this plant possess anti-inflammatory effects due to the content of oxylipines and caffeic acid derivatives, which are used in the treatment of arthritis [109]. In the case of *Harpagophytum procumbens*, much higher concentrations of the active principle harpagosid are necessary for the down regulation of iNOS expression in rat mesangial cells than are available in an effective concentration of the total extracts [110]. In another example, attempts to isolate the active components to prove the clinical efficacy from St. Johnswort (*Hypericum perforatum*), which is used as antidepressant, has not met with success [111,112]. In these cases, the application of the refined herbal extract rather than "isolated active principle(s)" may be favored, in order to benefit from the broad therapeutic and pharmacological action related to the special composition of the ingredients in the entire plant. Clinical and experimental examples of synergy have also been reviewed [113].

Evidence of substantial differences in the mode of action of a drug combination from the mode of action of the same drugs applied individually poses the question whether the search for the single active principles and, therefore, determination of marker constituents, in herbal medicines has any relevance. A new challenge is then directed toward understanding the effects of complex mixtures on molecular and biochemical processes in health and disease. The scientific validation of herbal medicines is further complicated by the fact that herbalists use preparations and mixtures which are not necessarily intended to target a particular organ, cell tissue, or biochemical system.

In order to achieve scientific and clinical validation of botanicals and herbal preparations, there is a need to adopt approaches using chemical standardization, biological assays, animal models, and clinical trials. Existing technologies are not adequate for complete analyses of constituents. In most developing countries, the costs of analyses and standardization are still too high, especially for small manufacturers. Furthermore, the non-availability of instruments and infrastructure, expertise, and human resources has hampered progress in standardization technology. A new paradigm on the concept of standardization and therapeutic validation of herbal medicines may be required to address the issues. The major challenge to the scientific community is, therefore, to formulate a simple, affordable, and reliable standardization method or protocol to be used in the standardization of herbal products.

5. DOCUMENTATION AND INTELLECTUAL PROPERTY RIGHTS

5.1 Introduction

The use of plants in the traditional medicine systems of many cultures has been well documented [114–116] but there remains a lot more information and knowledge scattered around in communities, families, tribes, and with local herbal medicine practitioners. Plant-based systems play an essential role in the healthcare of two-thirds of the world's inhabitants and an increasingly significant role in developed countries.

Ethnobotany and ethnopharmacology are interdisciplinary fields of research that look at the empirical knowledge of indigenous peoples concerning medicines and their potential health benefits and risks. Many of the plant-derived pharmaceuticals and phytomedicines currently in the market originate from the knowledge of these indigenous people, some of which has been documented, codified, or studied scientifically.

Indigenous knowledge in medicine is held either in the formal or in the nonformal sector. In the formal sector, recipes are documented to some extent in books by practitioners and sometimes in state-sponsored pharmacopoeia [117–119] or Materia Medica [120,121]. Pharmacopoeias are regularly published and provide information on drugs in some areas of herbal medicine, like TCM and Unani and Ayurvedic medicine. In the nonformal sector, knowledge held by indigenous communities often constitutes entire treatment regimes used by the community in their daily lives. There are also secret family-held recipes passed on from generation to generation. Given the effects of modernization, much of the knowledge in this sector will be lost to the world unless documented early.

Although indigenous knowledge systems can contribute to improvements in human health; skepticism about the efficacy of plant-based products is also justified in many instances. If indigenous knowledge systems are to play an important role in human health, not only must the inevitable claims be validated but also the ingredients, active constituents, and the methods used to validate the claim should be documented and made accessible to the consumer.

The absence of a satisfactory system for the protection of the intellectual property contained in traditional medicinal knowledge has been a constraint to the development of traditional medicine into a viable health system. The prominence given to intellectual property in the globalized world and the awareness that traditional knowledge had been exploited unfairly in the past has made holders of such knowledge wary of disclosure of the knowledge even to researchers in their own countries. The absence of an acceptable regime to protect IPR derived during the successful development of a known herbal product for commercialization has also prevented the participation of large companies in developing products based on traditional knowledge.

While scientific investigations on plants and plant parts used in indigenous medical systems can be rewarding, it must not be forgotten that many of the indigenous knowledge systems used in human disease treatment, including Ayurveda, Unani and Chinese traditional medicine, are based on holistic concepts unlike modern Western medicine. Herbal medicines may, therefore, be only a part of the treatment, and their specific role of correcting the imbalance of forces believed to cause the disease may not be related to allopathic medicinal perceptions of the disease, making allopathic bioassays irrelevant. Moreover, herbal medicines are made from many different plant parts, using long drawn-out complex processes often involving critical parameters. As such, there is no guarantee that a study of the principal components of an effective herbal medicine will provide information which could be exploited by the modern pharmaceutical industry.

Documentation of herbal medicine should involve documentation on the cultivation, harvesting, and technologies involved, including: plantation development and processing methods; the prior validation of products used in herbal medicine; documentation of the properties of synthetic products identical with or related to the active constituent(s) of the medicine; the chemistry of herbs believed to be responsible for the activity; the results of any clinical trials carried out on the product and aspects of marketing and trading; and legal issues including IPR. This is an unenviable task as only a fraction of the hundreds of thousands of plant species has been fully investigated in the laboratory.

In the West, the demand for herbal drugs, often derived from plants exported from developing countries, has been expanding in an unprecedented manner in recent years. The global craving for herbal products has serious implications for the survival of several plant species [122], and a large-scale program of cultivation should be initiated to replace herbal products which are unsustainably collected at the behest of manufacturers and exporters of herbal medicine. Conservation and cultivation methods must be developed and the information documented. In many cases, so little is known about the biology that the long-term effects of intensive harvesting are unknown, and, thus, informed decisions about regulating exploitation cannot be made easily.

The chemistry and efficacy of many of the plants are relatively unknown, and there is a distinct possibility of toxic effects and overdoses unless the secondary compounds are known and their activities understood. In double-blind, randomized, placebo-controlled trials, the value of even the most popular herbal supplements has been questioned. It has been concluded that the efficacy of ginseng root ex-

tract [123] for physical performance, immunomodulation, and some other claimed effects, and of *Ginkgo biloba* [124] for dementia or age-associated memory impairment has not been established beyond reasonable doubt.

5.2 Current status

While some documentation is available for herbal products in the formal sector, there is very little in the nonformal sector. Furthermore, even in the formal sector the drug dispensed by an indigenous medical practitioner may often not follow the protocol specified in the available documentation. Variations in raw materials used are inevitable, given that the chemical contents of plants vary in different cultivars and may change with the location, age of the herb collection, the part used, storage conditions, period of storage, and method of drying. The efficacy of formulations depends on the manufacturing procedure, concentration of the chemical constituents, and the solvent for extraction. It is clear that chemical standardization is the way forward, if herbal remedies are to be widely used.

Information on the chemistry of plants used in herbal products, which is important for quality control, standardization, and the development of new Western drugs, is being well documented in journals but is rarely available at a single location for easy reference. There is even less information on herbal dietary supplements, which are now being accessed by large sections of the populations of developed countries. Claims, often with no real basis, are made for their efficacy. Manufacturers of dietary supplements should be encouraged to publish a pharmacopoeia-like "nutracopoeia" giving details on preparation, active constituents, efficacy studies, and chemical and clinical data on nutraceuticals.

Although there has been some attempt at documenting herbal medicines, there is a lacuna in this area which needs to be filled. At the international level, WHO has developed a strategy to review traditional medicines, including a program to develop monographs for herbal ingredients.

Much of the data on herbal medicines is made available in several databases, which specialize in the area of herbal medicines. Amongst the databases available, some are a collection of traditional beliefs in folk medicine and alternative healthcare like the Online Archive of American Folk Medicine [125], administered by the University of California, Los Angeles. Data collected from indigenous communities have been collated in similar databases maintained by nongovernmental organizations, but they are not yet publicly available due to intellectual property concerns. Many databases are proprietary and provide information on indications, actions, and active constituents to herbal medicine practitioners in the West, e.g., the Phytotherapies database [126] and the Natural Medicines Comprehensive Database [127]. Some claim to provide impartial evidence-based information, like the nonprofit HerbMed website [128].

Databases have been sponsored by governments of some developing countries. A commercial database containing 550 000 records of TCM, also including areas related to Tibetan medicine, is available [129]. The Indian government is setting up a Traditional Knowledge Digital Library, which would be a knowledge repository of Indian traditional knowledge in Ayurvedic, Unani, and Siddha medicine and yoga [130].

Some general databases containing reports on herbs include AGRICOLA of the U.S. Department of Agriculture [131]. Some, like AltHealth Watch [132] and the MANTIS [133] database, contain material on alternative medicine and herbal medicine collated from magazines and journals. Similarly, MICROMEDEX [134] claims to provide a source of referenced scientific information about complementary and alternative therapies and practices.

Many government databases contain reports of chemical investigations and clinical studies on herbal medicine. They include CRISP (Computer Retrieval of Information on Scientific Projects) [135] which is a searchable database of U.S. federally funded biomedical research projects and clinical trials at <www.clinicaltrials.gov>, which provides regularly updated information about federally and privately supported clinical research on human volunteers in the United States.

The Cochrane Collaboration, an international not-for-profit independent organization, provides information [136] reviewing the effects of healthcare including herbal medicine and evidence provided by clinical trials and other interventions. EMBASE, maintained by the publisher Elsevier [137], a database with 18 million records covering MEDLINE records as well, collates information from over 5000 biomedical journals on medical and drug-related subjects. NAPRALERT, maintained by the College of Pharmacy, University of Illinois at Chicago, contains information on ethnomedicine and natural products published in journals. It has about 180 000 records which contain information on academic research carried out in pharmacology, biological activity, and chemistry of natural products. Information on NAPRALERT is available at its website [138].

The International Bibliographic Information on Dietary Supplements (IBIDS) database [139] specializes in dietary supplements and provides access to bibliographic citations and abstracts from published, scientific literature on supplements and also reports on any adverse effects.

Adverse reports on the use of herbal medicines are also recorded in the ESCOP database [140], maintained by the European Scientific Co-operative on Phytotherapy (ESCOP).

5.2.1 Intellectual property rights

Most countries have had their own herbal medicine system but they are constantly being improved with input from abroad, in the form of training for practitioners on the medicinal systems of other countries or the adoption of "effective" treatments from abroad or from systems brought in by migratory populations. Most transfers also involved the growing of exotic plants used in these preparations from imported material or the regular import of such plants or plant material.

Modern biotechnological techniques can be used to enhance yields of plant products from existing sources, to develop new sources for them, and to design new products with better biological properties, but these require access to both biological resources and the traditional knowledge of indigenous communities. Biological resources are unevaluated, and their habitats, usually in the developing countries, are at risk, leading to extinction and loss of valuable species. Traditional knowledge of local communities is also being rapidly lost, both through the loss of traditionally used biological resources by overexploitation and changes in the life styles of indigenous peoples.

Developing countries and indigenous communities have, moreover, been made apprehensive of acts of biopiracy through which communities have lost control over their intellectual property and also made to expect unrealistic levels of compensation for their traditional knowledge by nongovernment organizations. During the past 25 years, the prominence given to intellectual property has convinced the owners of biological resources that these resources are valuable, as they are part of a national or community heritage and no longer the common heritage of the people of the world, and that the national or community heritage has to be protected from undue exploitation.

The Convention on Biological Diversity (CBD) [141] was negotiated to provide an incentive to developing countries for the sustainable use of biodiversity. The CBD also created an environment which could facilitate research on the biodiversity of developing countries by providing for access to genetic resources and the sharing of any benefits derived from their exploitation. Countries and communities owning biological resources were expected to obtain an equitable share of the profits and the transfer of the technology and know-how in return for permitting the exploitation of their genetic resources and associated traditional knowledge by other countries on mutually agreed terms (MAT). The CBD was expected to usher in a new era in natural products drug discovery and development. One hundred and eighty-eight states and the EU have ratified the Convention so far.

Although most countries are members of the CBD, very few have introduced legislation in conformity with the Convention and there are few successful working models at present that ensure an equitable distribution of benefits accruing from exploitation of traditional knowledge. Part of the problem is that there are two powerful international fora other than the CBD dealing with these issues, the World Trade Organization (WTO) and the World Intellectual Property Organization (WIPO).

One of the problems facing developing countries in protecting their biodiversity from unethical exploitation is the absence of a mechanism to protect herbal medicines in the IPR regime which most developing countries have put or are putting into place to conform to WTO's Trade Related Intellectual Property Rights (TRIPS) agreement. TRIPS does not permit the patenting of herbal medicines, only plants or compounds with new biological activities or the biological activity itself being considered patentable. The herbal medicine and its preparation cannot be patented as much of the knowledge involved is not novel and in the public domain. Although there is a general understanding that there should be a satisfactory mechanism for the protection of traditional knowledge and many suggestions have been made, none have achieved acceptance. It is generally held that successful protection will require changes to TRIPS.

5.3 Constraints and challenges

None of the databases presently available provides comprehensive information on herbal medicine. Knowledge available in indigenous knowledge systems and in the nonformal sector regarding herbal medicine is often inaccessible as the owners of the knowledge are wary of the consequences of disclosure. There is no mechanism to collect and record data on the plants and the processing and formulation methods used in herbal medicines. Although there is some documentation of herbal medicine in the formal sector, herbal medicines produced by individual medical practitioners or commercial organizations do not often conform to recipes recorded in national pharmacopoeia. The herbs used in the formulation may differ, the content of the active constituent varies widely, and the processing methods are rarely uniform.

Indigenous communities and family practitioners should be assured that their IPR will not be unfairly exploited. Amongst the most important constraints to successful documentation and dissemination of such knowledge is the non-availability of a suitable mechanism which could ensure that the IPR of owners of this knowledge will be protected and that their formulations will not be copied. Existing IPR laws should also be modified to permit the patenting of new drugs developed from traditional herbal medicines in order to attract multinational pharmaceutical companies to the field and thereby increase research and development in herbal medicine. Although herbal medicines, prepared according to established pharmacopoeia like the Auyrveda, Unani, or TCM cannot be patented, new composition and processes of herbal drugs have been patented [142–144]. Also, there have been several patents granted in developed countries on active compounds isolated from plant sources that have sometimes been transferred from developing countries, thus surreptitiously attracting charges of biopiracy.

Some patents on the activity of herbal products and medicines, like that on the healing effects of turmeric (now cancelled) were granted in the West, although the knowledge has been in the public domain in the East for hundreds of years. The Indian government is setting up a Traditional Knowledge Digital Library Database [130] containing Indian traditional knowledge in Ayurvedic, Unani, and Siddha medicine, which may be used by patent examiners in an attempt to provide them with access to Indian traditional knowledge and thereby to prevent the granting of such patents in the future.

In order to proceed with the validation of the efficacy of medicinal plants, WHO believes that several levels of evidence including ethnobotanical claims, anecdotal information, pharmacological studies, and observational studies should be taken into account [145,146]. A major constraint to standardization and assuring safety/efficacy is the absence of monographs on individual medicines. The world has recognized the need to provide less rigorous routes for the acceptance of herbal medicine with documentary evidence of long usage being accepted as evidence for safety. The German Commission E, for example, provided for evaluation of herbal medicine in traditional use for over 30 years to be relegated to monographs published by the Commission. Such monographs have helped manufacturers in developing countries to obtain approval for marketing their products in developed countries.

Sufficient care is not being taken to ensure that plant species used in herbal medicine are being conserved. Habitats in which they grow are not protected, and there are insufficient programs for the

conservation of threatened plant species through the preservation of germ plasm and the promotion of cultivation.

5.4 Recommended protocols

It is desirable to establish a document database containing information on each approved medicinal herb or herbal medicine. A central digital document database which is regularly updated and which contains this information with linkages to references in other databases like NAPRALERT should be established for easy access by all beneficiaries, producers, and stakeholders. The knowledge base for an herb or herbal medicine, promoted for wider use, should be strengthened and expanded so that there is a sound scientific basis for each use. This would require the presentation of data for each herb, used in herbal medicine including:

- plant identification, including cultivar with voucher specimen
- plant, preferably voucher stored in a herbarium, for future reference
- age of the herb (maturity/flowering plant, etc.)
- location of cultivation, including altitude and longitude/latitude (GPS)
- fertilizers/pesticides used, if any
- time of harvest, including time after application of pesticides (if applicable)
- storage conditions of the plant, before sale
- drying process
- certificate, confirming the above

Apart from details on each herb, details regarding the manufacture of the herbal medicine including the following data should be made available:

- protocol or pharmacopoeia or method used for producing the medicine
- plant or plants (for multi-plant herbal medicine) used
- part of plant used in medicine
- vehicle used for producing drug/medicine, e.g., alcohol or water (with composition if a mixed solvent); type of preservative used, if any, and amount

Where plants are purchased, documents maintained by the supplier regarding the herb should be made available by the manufacturer.

- Prepare monographs for traditionally used herbal medicines in a suitable format.
- Legislate to ensure that manufacturers provide relevant data on herbs and manufacturing processes.
- Initiate programs to conserve biological resources.
- Work toward amending TRIPS to include protection of IPR contained in indigenous knowledge and to make the development of herbal medicines attractive to pharmaceutical companies.
- Legislate to establish standards in herbal medicine manufacturing and ensure their implementation.
- Patents involving biological resources should be granted only if the source of material is specified and reference made to the material transfer agreement. Where pharmaceutical companies are prepared to develop herbal medicines into standardized novel preparations with proven efficacy, the companies could be provided with IPR, while assuring other stakeholders of a fair share of benefits on the basis of efficacy or shelf-life being an inventive step.

As most herbal medicines are prepared from more than one plant material, it is imperative that documentation should be made both on single medicinal plants and on composite herbal preparations.

5.4.1 Single plants

- plant identification: family, genus, species (including cultivar, if any) with synonyms and older names where applicable; English (common) name(s); local name
- herbarium voucher; specimen number and date with collector's name and identity
- age of the herb (maturity/ flowering plant, etc.)
- location of cultivation/collection including altitude and longitude/latitude (GPS)
- fertilizers/pesticides used (if any)
- time of harvest including time after application of pesticides (if applicable)
- storage conditions of the plant before sale
- drying process
- certificate confirming the above

5.4.2 Composite herbal medicine

Apart from details on each herb as outlined for single plant, details regarding the manufacture of the composite herbal medicine, including the following data, should be made available:

- protocol or pharmacopoeia or method used for producing the medicine
- plant or plants (for multi-plant herbal medicine) used
- part of plant or plants used in the medicine
- vehicle used for producing the drug/medicine, e.g., alcohol or water (with composition if a mixed solvent); type of preservative used, if any, and amount
- excipients (if any) used, amount
- major constituents: carbohydrates, protein, fat, dietary fiber, inorganic material, binder, total energy value per mass (kcal/g or kJ/g)
- suggested dose, number of times to be used, how many days to be used
- probable side effects/precautions to be taken, contraindications, restrictions for children, pregnancy, nursing mothers, etc.
- storage: at x °C, room temperature, away from heat, sun, etc.
- stability; shelf life; best before date
- cautionary note, if any

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7. ACRONYMS

ACE angiotension converting enzyme

AGRICOLA The National Agricultural Library Catalogue of the USDA

AIDS acquired immunodeficiency syndrome
API Ayurvedic Pharmacopoeia of India

BCE before Christian era

BHP British Herbal Compendium
CBD Convention on Biological Diversity

CE capillary electrophoresis

CPMP Committee for Proprietary Medicinal Products

CRISP Computer Retrieval of Information on Scientific Projects

EC European Community
ECD electron capture detector

EEC European Economic Community
ELSD evaporative light scattering detector
EMEA European Medicines Agency

ESCOP European Scientific Cooperative on Phytotherapy

FD fluorescence detector

FDA U.S. Federal Drug Administration

FID flame ionization detector GC gas chromatography GPS global positioning system

HPLC high-performance liquid chromatography

IBIDS International Bibliographic Information on Dietary Supplements ICDRA International Conference on Drug Regulatory Authorities

ICP–MS inductively coupled plasma–mass spectrometry

ICP-OES inductively coupled plasma-optical emission spectrometry

IPR intellectual property rights
iNOS inductive nitrogen oxide synthase
JSHM Japanese Standards for Herbal Medicines

LC-NMR liquid chromatography-nuclear magnetic resonance spectroscopy

LC-UV-MS liquid chromatography-ultraviolet-mass spectrometry

MAE microwave-assisted extraction

MANTIS Manual Alternative and Natural Therapy Index System

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MAT mutually agreed terms

MD Maryland

MEDLINE The online database of the U.S. National Library of Medicine

MICROMEDEX Thompson Healthcare Solutions Database

MS mass spectrometry

NAPRALERT Natural Product Alert (database)

NMR nuclear magnetic resonance spectroscopy

NO nitrogen oxide

PC paper chromatography
PCA principal component analysis
PHWE pressurized hot water extraction
PLE pressurized liquid extraction
PRC People's Republic of China

QC quality control RI refractive index

SFE supercritical fluid extraction

SIMCA simulated independent modeling of class analogy

TCM traditional Chinese medicine

TDR tropical diseases research and training

TGA Therapeutic Goods Administration (Australia)

TLC thin layer chromatography

TRIPS trade-related intellectual property rights

UK United Kingdom

UNICEF United Nations International Children's Emergency Fund

UNDP United Nations Development Program

USA United States of America
USDA U.S. Department of Agriculture

USEPA U.S. Environmental Protection Agency

USP U.S. Pharmacopoeia

UV ultraviolet

WTO World Trade Organization