

Herbal Medicines

Research and evaluation of traditional and herbal medicines

The expanding use of traditional and herbal medicines is gaining recognition globally. Not only do herbal medicines continue to be used in primary health care in developing countries, but they are also increasingly popular in those countries where conventional medicine is predominant. With this expansion in use beyond national boundaries, the safety, efficacy and quality control of herbal medicines and traditional therapies have become important concerns for health authorities and the public. The difficulty of regulation is particularly challenging given the development of traditional medicine by different cultures in different regions in the absence of a parallel development of international standards and appropriate methods of evaluation.

Consequently, governments, researchers and manufacturers are increasingly in need of standards, technical guidance and information to assist them in determining how research and evaluation of traditional and herbal medicines should be carried out. Since 1991, WHO has published a series of technical guidelines on traditional medicine which are particularly relevant to current needs. WHO's latest document in the series, *General Guidelines for Methodology on Research and Evaluation of Traditional Medicine*,* has been developed as a comprehensive guide to methodologies to be used when carrying out research involving the use of herbal medicines and traditional procedure-based therapies.

It includes sections on research and evaluation of herbal medicines and traditional procedure-based therapies, clinical research, and related issues such as ethics, education, training and surveillance. The following text has been adapted from the guidelines.

The methodologies for research and evaluation of traditional medicine should guarantee the safety and efficacy of herbal medicines and traditional procedure-based therapies without becoming obstacles to the application and development of traditional medicine generally.

Methodologies for research and evaluation

Traditional medicine involves the use of herbal medicines, animal parts and minerals. However, herbal medicines are the most widely used of the three. The *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine* cover a wide range of issues and are intended to meet the different situations that exist in various countries and regions of the world. The guidelines can be modified to meet the specific needs of countries. Where appropriate, a phased approach to the implementation of the guidelines should be considered. They are intended particularly to serve as a reference source for researchers, health care providers, manufacturers, traders, and health authorities.

Definitions

Certain definitions concerning herbal medicines are set out in the *Guidelines for the Assessment of Herbal Medicines* (1) and *Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines* (2). In order to make WHO definitions consistent, certain terms have now been harmonized to meet the demand for the establishment of standard, internationally accepted definitions for use in the evaluation and research of herbal medicines.

Herbs

Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

* *General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine*. World Health Organization, WHO/EDM/TRM/2000.1. The guidelines have been formulated in collaboration with national drug regulatory authorities and scientists from many countries worldwide, members of the WHO Expert Advisory Panel on Traditional Medicine and WHO Collaborating Centres on Traditional Medicine. A WHO informal consultations on Research Methodology for Evaluation of Traditional Medicine, was held at the National Institutes of Health in the United States, in 1997 prior to drafting of the document, which was later finalized at a WHO consultation, Hong Kong SAR, China in April 2000.

Herbal materials

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.

Herbal preparations

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

Traditional use of herbal medicines

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations. Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities.

Therapeutic activity

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses; improvement of symptoms of illnesses; as well as beneficial alteration or regulation of the physical and mental status of the body.

Active ingredients

Active ingredients refer to ingredients of herbal medicines with therapeutic activity. In herbal medicines where the active ingredients have been identified, the preparation of these medicines

should be standardized to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

Botanical verification and quality considerations

The first stage in assuring the quality, safety and efficacy of herbal medicines is identification of the plant species by botanical verification. The information required includes the currently accepted Latin binomial name and synonyms, vernacular names, the parts of the plant used for each preparation, and detailed instructions for agricultural production and collection conditions according to each country's good agricultural practice. Detailed information is presented in *WHO Quality Control Methods for Medicinal Plant Materials* (3) and *WHO Monographs on Selected Medicinal Plants* (4).

Research and evaluation of safety and efficacy

Research and evaluation of herbal medicines that do not have a long history of use or which have not been previously researched, should follow WHO's *Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines* (2). For herbal medicines with a well-documented history of traditional use, the following procedures may be followed.

Literature review

In assessing the safety and/or efficacy of a herbal medicine, whether derived from a single plant or from a defined mixture of plants, the first step involves the evaluation of literature reports. The literature search should be made using reference books, review articles, systematic surveillance of primary sources, and/or database searches. If it is felt that reference books and review articles might contain inaccurate information, primary references should be consulted for in-depth analysis. The search profile used should then be recorded and the search be extended to gather information on closely related plant species for chemotaxonomic correlation.

If several investigators publish similar safety and/or efficacy data, they should be accepted as useful indicators. In vitro biochemical or cellular safety data should be viewed as indicators of potential toxicity, but not as absolute markers. In vivo data from animal studies are more indicative of toxicity

and may be considered to be safety markers. For both safety and efficacy, a pharmacological effect observed in vitro or in animal models is not necessarily applicable to humans. In vitro data usually serve to verify the reported mechanism of action in animals or humans. Such data have to be confirmed by clinical studies. Well-documented reports of pharmacological activity in animals or humans may be viewed as having scientific rationale.

Theories and concepts of systems of traditional medicine

The theories and concepts of prevention, diagnosis, improvement and treatment of illness in traditional medicine may rely on a holistic approach towards the sick individual, and disturbances will also be treated on the physical, emotional, mental, spiritual and environmental levels simultaneously. As a result, most systems of traditional medicine may use herbal medicines or traditional procedure-based therapies along with certain behavioural rules promoting healthy diets and habits. Holism is a key element of all systems of traditional medicine. Therefore, when reviewing the literature on traditional medicine (both herbal medicines and traditional procedure-based therapies), the theories and concepts of the individual practice of traditional medicine, as well as the cultural background of those involved, must be respected.

Review of safety and efficacy literature

A review of the literature should identify the current level of evidence for the safe and effective use of a herbal medicine. In cases where the traditional uses and experience of a herbal medicine in humans have not established its safety and efficacy, new clinical studies will be necessary. If well-known herbal medicines are formulated into a new mixture, however, the requirements for proof of safety and efficacy should take into account the established uses of each herbal medicine. Such information may appear in authoritative national documents such as pharmacopoeias or official guidelines of national authorities, or in scientific publications. However, it should not be forgotten that new preparative methods may alter the chemical, toxicological and even pharmacological profiles of traditionally used herbal medicines.

Safety

Reported and documented side-effects that have been recorded according to established principles of Pharmacovigilance of a herb or herb mixture, its

closely related species, constituents of the herb and its preparations/finished herbal products should be considered when decisions are made about the need for new pharmacological or toxicological studies.

The absence of any reported or documented side-effects is not an absolute assurance of safety for herbal medicines. However, a full range of toxicological tests may not be necessary. Tests which examine effects that are difficult or even impossible to detect clinically should be encouraged. Suggested tests include immunotoxicity, genotoxicity, carcinogenicity and reproductive toxicity.

When there is no documentation of historical use of a herbal medicine, or when doubts exist about its safety, additional toxicity studies should be performed. Where possible, such studies should be carried out in vitro. Using in vitro tests can reduce the number of in vivo experiments. If in vivo studies are needed, they are to be conducted humanely, with respect for the animals' welfare and rights. Toxicity studies should be conducted in accordance with generally accepted principles, such as those described in WHO's *Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines* (2).

Efficacy

It is important for herbal medicines, and particularly for those made from a mixture of herbal products, that the requirements for proof of efficacy, including the documentation required to support the indicated claims, should depend on the nature and level of the indications. For the treatment of minor disorders, for non-specific indications, or for prophylactic uses, less stringent requirements (e.g. observational studies) may be adequate to prove efficacy, especially when the extent of traditional use and the experience with a particular herbal medicine and supportive pharmacological data are taken into account.

The level of the evidence and the grading of recommendations must correspond to the nature of the illness to be treated or the nature of the physical or mental function to be influenced and regulated. Definitions of levels of evidence and the grading of recommendations from the USA Agency for Health Care Policy and Research may be used for guidance (5). Many other national documents, such as the Australian guidelines for levels and kinds of evidence to support claims for therapeutic goods (6) will also provide a reference.

The therapeutic alternatives available within the community and the risks of the herbal in question have to be taken into account. It should be noted that in the case of herbal medicines made from herb mixtures, a therapeutic or scientific rationale must exist for the presence of each herb in the mixture. Research studies on the possible therapeutic effects of herbal medicines made from herb mixtures or specific combinations of herbs, however, need to be conducted.

Clinical studies

The scope and design of such studies should be based on information of traditional use obtained from official national compendia and relevant literature, or by consultation with traditional medical practitioners.

In the case of a new herbal medicine, a new indication for an existing herbal medicine, or a significantly different dosage form or route of administration, the general principles and requirements for a clinical trial should follow as closely as possible to those which apply to conventional drugs, such as guidelines for good clinical practice (7–8). In some cases, however, the design of such studies must be adapted to deal with the particularities of herbal medicines.

Well-established, randomized controlled clinical trials provide the highest level of evidence for efficacy. Such studies facilitate the acceptance of herbal medicines in different regions and in people with different cultural traditions. However, methods such as randomization and use of a placebo may not always be possible as they may involve ethical issues as well as technical problems. For example, it may not be possible to have a placebo control if the herbal medicine has a strong or prominent smell or taste, as is the case for products containing certain essential oils. In addition, patients who have been treated previously with the herbal medicine under investigation with a characteristic organoleptic property, cannot be randomized into control groups. In the case of herbal medicines with a strong flavour, placebo substances with the same flavour may have a similar function. In such cases, it may be advisable to use a low dosage of the same herbal medicine as a control.

Observational studies involving large numbers of patients may also be a very valuable tool for the evaluation of herbal medicines. According to the theories and concepts of traditional medicine, the prevention, diagnosis, improvement and treatment of illness is often based on the specific needs of the

individual patient. Therefore, single-case studies for the evaluation of efficacy of a herbal medicine should not be ignored.

Regulatory requirements of national authorities for evaluating herbal medicines differ from country to country. Many governments have recently developed their own national regulations for traditional medicine. For an extensive review of the regulatory situation in various countries, consult WHO's *Regulatory Situation of Herbal Medicines: a Worldwide Review* (9).

Research

Normally, clinical research of all types of conventional and traditional medicine considers both efficacy and safety, and is conducted in line with WHO's *Guidelines for Good Clinical Practice* and the *Declaration of Helsinki* (7).

The infrastructure for research in traditional medicine is significantly less developed than that for conventional medicine. However, there is now an increasing demand that the safety and efficacy of traditional medicine be determined so that it can be considered by the public. In the development of traditional medicine, it is important that support be given to the establishment of appropriate infrastructures.

Other pragmatic issues that require consideration include funding, facilities, and involvement of properly trained research personnel and traditional medical practitioners. Clinical research must be carried out under conditions which ensure adequate safety for the subjects. The institution selected must have adequate facilities, including laboratories and equipment, where necessary, and sufficient clerical, medical and allied health workers to support the study as required. Facilities should be available to meet any emergencies.

If a multicentre study is necessary, this may require a special administrative system to ensure that the study is conducted simultaneously and adequately at different sites by several investigators following the same protocol. It will be necessary to train investigators from different sites to follow the same protocol, and to standardize methods of patient selection, termination of patient participation, administration, and data collection and evaluation. Appropriate consultation about the statistical analysis is necessary during the planning, execution and assessment phases to ensure methodological consistency.

Ethics

The *CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects* (10) should be implemented in each clinical trial. An institutional or national ethics committee should review each trial.

Education and training

All health care providers of traditional medicine should be encouraged and required to have proper training in both traditional and conventional medicine, as their training and skills will affect the safety and efficacy of the treatment. The practitioners' knowledge and skills need to be continuously upgraded to enable them to engage in clinical research within their own individual speciality.

Surveillance systems

According to the situation of traditional medicine in a particular country, governments may need to establish national surveillance systems at different levels of the health sector to monitor and evaluate any adverse effects of herbal medicines. Knowledgeable researchers and practitioners of traditional medicine should be consulted during the development of such systems.

The evaluation of adverse effects needs to be based on appropriate methods of determining causality. Such methods include instruments to determine adverse events experienced by target groups (patients and practitioners), prospective and retrospective studies to determine adverse effects in specific settings, and post-marketing surveillance of herbal medicines.

References and further reading

1. World Health Organization. *Guidelines for the Assessment of Herbal Medicines*. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Technical Report Series, No. 863 (1996).
2. World Health Organization Regional Office for the Western Pacific. *Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines*. Manila, 1993.
3. World Health Organization. *Quality Control Methods for Medicinal Plant Materials*. Geneva, 1998.
4. World Health Organization. *WHO Monographs on Selected Medicinal Plants. Volume I*. Geneva, 1999 (Volume 2 in press).
5. Agency for Health Care Policy and Research. *Definitions of Levels of Evidence and the Grading of Recommendations*. Washington, USA 1992.

6. Therapeutic Goods Administration. *Guidelines for Levels and Kinds of Evidence to Support Claims for Therapeutic Goods*. Woden, Australia, 2000.

7. World Health Organization. *Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. The Use of Essential Drugs*. Technical Report Series, No. 850 (1995).

8. The ICH Harmonized Tripartite Guideline for Good Clinical Practice produced by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1996.

9. World Health Organization. *Regulatory Situation of Herbal Medicines: a Worldwide Review*. WHO/TRM/98.1. Geneva, 1998

10. Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, 1993.

The safety of herbal medicines

The use of herbal medicines poses sensitive challenges to drug regulatory authorities responsible for the safety, efficacy and quality of medicines both nationally and internationally. An informative presentation on these issues was made by the WHO Programme on Traditional Medicines at the Twenty-third Annual Meeting of National Centres participating in the WHO International Drug Monitoring Programme held in Tunisia in November 2000.

The use of medicinal plants is accepted as the most common form of traditional medicine. Among the entire flora, it is estimated that 35 000 to 70 000 species have been used for medicinal purposes. Some 5000 of these have been studied in biomedical research. In developing countries, herbal medicines continue to play an important role in primary health care, especially where coverage of health services is limited. In industrialized countries, herbal medicines are increasingly popular. However, the expanded use of herbal medicines has led to concerns relating to assurance of safety, quality and efficacy. The four major steps to overcome concerns have been identified as:

- Regulation and registration of herbal medicines.
- Quality control of herbal medicines and materials.
- Rational use.
- National surveillance systems to monitor and evaluate adverse reactions.

The regulatory situation differs from country to country and herbal medicines may be classified as prescription only, proprietary drug products, food supplements or foods, although, in general, the majority of herbal medicines have no regulatory status. It is therefore important that the manufacture of herbal medicines and related products moving in international commerce needs to be governed by similar standards of safety, quality and efficacy as those required for pharmaceutical products. In this respect, proof of safety should always take precedence over establishment of efficacy.

In order to facilitate the development of national regulation and registration of herbal medicines, WHO has published a *Regulatory Situation of Herbal Medicines: a Worldwide Review* containing regulatory information from 50 countries (1). WHO has also published *Guidelines for the Assessment of Herbal Medicines* (2) and *General Guidelines on Methodologies for Research and Evaluation of Traditional Medicine* to assist countries in the evaluation of herbal medicines (3).

Quality will influence safety, and often depends on the quality of the raw materials employed. A review of published adverse drug reactions of herbal medicines has identified the main cause of such events to be contamination and adulteration. Quality assurance is vital (4). WHO has published *Quality Control Methods for Medicinal Plant Materials* to support countries in developing national standards (5). In addition, an increasing number of national and regional pharmacopoeias include monographs on herbal materials.

Some common examples of problems involved with nomenclature of herbal medicines were also presented by the Uppsala Monitoring Centre during the meeting. Lack of correct identification of herbal medicines was targeted as a common pharmacovigilance problem, so that the botanical verification and identification of herbal medicines was seen as a fundamental step towards ensuring safety.

Each plant should be identified according to the Latin binominal name. As an example, nomenclature problems can be illustrated by the confusion centred around the name *Ginkgo biloba*. Although there is only one species of *Ginkgo*, there are several synonymous names (*Pterophyllus*, *Salisburia*) and many common names. Furthermore, the leaves contain various flavonoid glycosides and the seeds contain various alkaloids, so that differentiation between leaves and seeds is

very important. Ingredients are detailed in the Uppsala Monitoring Centre data base as "Ginkgo leaves extract" but, depending on the method of extraction, different active ingredients will be obtained. Certain other related products are also described as *Ginkgo biloba* in the Uppsala Monitoring Centre data base. In addition, there is also Ginkor which comprises a mixture of ginkgo and troxerutin. *Ginkor proto* contains three ingredients, as does Friggs ginkgo *Aristolochia*. Although there are about 500 species, the Uppsala Monitoring Centre data base has only one report entry.

Following the presentations, a working group was convened which proposed that the definition of herbal medicines, for the purposes of pharmacovigilance, should be extended to include "labelled and unlabelled plants and traditional medicines from animal and mineral origin" as set out in the *WHO Guidelines for the Assessment of Herbal Medicines* (2). Discussion also took place on evaluation of herbal products based on safety quality and efficacy, registration and regulation adapted to the needs of individual countries, and development of reliable sources of information.

In monitoring the safety and efficacy of herbal medicines, education and communication are very important and the respective roles of the Uppsala Monitoring Centre and WHO in achieving this were emphasized.

The following recommendations were also made by the working group:

- A monitoring and surveillance system for herbal medicines should be developed in each country.
- Basic information should be made available to all countries, and access improved to international data bases.
- Pharmacovigilance activities should be strengthened between the WHO Programme on Traditional Medicines and the Uppsala Monitoring Centre.
- Adverse drug reaction reporting forms for herbal medicines should be in a similar format as those currently used for pharmaceuticals.
- Education of health professionals on the rational use of herbal medicines should be carried out by qualified herbalists.

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- Public information and educational tools for consumers should be developed.
 - Collaboration with poison control centres should be established.
 - Health authorities should promote the development of pharmacognosy.

These recommendations will be implemented by the WHO Traditional Medicines Programme in collaboration with other partners in the WHO International Drug Monitoring Programme, and progress will be reported at the next Annual meeting of National Centres in November 2001.

References

1. World Health Organization. *Regulatory Situation of Herbal Medicines: a Worldwide Review*. WHO/TRM/98.1. Geneva, 1998.
2. World Health Organization. *Guidelines for the Assessment of Herbal Medicines*. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Technical Report Series, No. 863, 1996.
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4. World Health Organization. *Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicinal products*. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Technical Report Series, No. 863, 1996.
5. World Health Organization. *Quality Control Methods for Medicinal Plant Materials*. Geneva, 1998.