

## Original Article

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# Herbal Medicine Today: Clinical and Research Issues

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Herbal medicine is the use of medicinal plants for prevention and treatment of diseases: it ranges from traditional and popular medicines of every country to the use of standardized and triturated herbal extracts. Generally cultural rootedness enduring and widespread use in a Traditional Medical System may indicate safety, but not efficacy of treatments, especially in herbal medicine where tradition is almost completely based on remedies containing active principles at very low and ultra low concentrations, or relying on magical-energetic principles.

In the age of globalization and of the so-called 'plate world', assessing the 'transferability' of treatments between different cultures is not a relevant goal for clinical research, while are the assessment of efficacy and safety that should be based on the regular patterns of mainstream clinical medicine.

The other black box of herbal-based treatments is the lack of definite and complete information about the composition of extracts. Herbal derived remedies need a powerful and deep assessment of their pharmacological qualities and safety that actually can be realized by new biologic technologies like pharmacogenomic, metabolomic and microarray methodology. Because of the large and growing use of natural derived substances in all over the world, it is not wise to rely also on the tradition or supposed millenarian beliefs; explanatory and pragmatic studies are useful and should be considered complementary in the acquisition of reliable data both for health caregiver and patients.

**Keywords:** evidence based medicine – explanatory trials – herbal medicine – mainstream medicine – phytotherapy – pragmatic trials – traditional medical system – traditional medicine

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Herbs are natural products and their chemical composition varies depending on several factors and therefore varying from people to people, from energetic decoctions to the use of herbal extracts following Western methodologies of mainstream medicine. Traditional medicines has a very long history: it is the sum total of the practices based on the theories, beliefs and experiences of different cultures and times, often inexplicable, used in the maintenance of health, as like in the prevention, diagnosis, improvement and treatment of illnesses.

In every country traditional medicines find foundation in magical or religious beliefs, or popular experience and

the World Health Organization is engaged to establish definitive guidelines for methodology of clinical research and the appraisal of effectiveness of traditional medicine

## European Traditional Herbalism

For centuries traditional medical systems (TMS) were the primary medical system in the countries of origin, and now nevertheless the present dominance of the Western scientific medical model, citizens and health-caregivers are starting to rely and trust TMS substituting conventional scientifically proved therapies with unconventional ones. Generally cultural rootedness enduring and widespread use of TMS may indicate safety, but not the efficacy of the treatments especially in herbal medicines where tradition is almost completely based on remedies containing active principles at very low and ultra low

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concentrations, or relying on magical-energetic properties of sun, moon, etc.

In European traditional herbalism categories similar to Asiatic medicines, referring to 'humoral-energetic doctrines' that has qualities (like heat, cold, dry, humid), and elements (fire, air, water, earth, etc.) are used. European popular medicine still counsel the so-called depurative plants for treatment of dermatological illnesses, like psoriasis or eczemas, like it were due to intoxications, as well as diuretic plants for arthritis, or a decoction of *Stachys* (called 'herb of fear') used as bath to wash out fears, or hay baths as treatment of cancer.

A discussion on methodologies for research and evaluation of traditional medicine should be divided in two parts: herbal medicines and traditional procedure-based therapies.

Herbal medicine has become a popular form of healthcare; even though several differences exist between herbal and conventional pharmacological treatments, herbal medicine needs to be tested for efficacy using conventional trial methodology and several specific herbal extracts have been demonstrated to be efficacious for specific conditions. Nevertheless the public is often misled to believe that all natural treatments are inherently safe, herbal medicines do carry risks, so research in this area must be intensified. The main question that has not been often answered satisfactorily deal with the triad absorption/metabolism/efficacy of herbs and their extracts and is actually an important unsolved problem in judging their many alleged health effects (1).

Mind-body medicine can be considered as a complementary or an alternative mode to traditional Western medicine, and a variety of other modes of interventions that are presently used in a CAM paradigm may act in large part via the mind-body connection (2); and in this sense trusting in the traditional principles of a medicine that is deeply rooted in a culture can represent a type of mind-body connection having a real pharmacological activity through a placebo like effect. So a successful treatment is often the consequence of both types of treatments acting synergistically, nevertheless efficacy assessment of traditional medicines cannot be different from that of conventional medicine.

Long-term use of medicinal herbs enables a process of selection but limited and only partial, of short and medium-term safe remedies, that however does not match with modern issues relatives to the interferences with synthetic drugs. Treatment selection is often limited because of the multiple meaning of efficacy in relation to pathology and diseases in different cultures. The transfer of a medical concept to a new country may be really misleading and lead to deep modifications of its medical-therapeutic and cultural essence, especially if a remedy is part of a TMS, and modifications follow adaptation to local conditions and cultural habits. These modifications may deeply vary in extension, but probably

**Table 1.** Traditional vs. Scientific knowledge

Traditional Use of Herbs	Scientific Use
<ul style="list-style-type: none"> <li>• Every people use typical plants or parts of these, often with different indications, as juices, decoction or pills.</li> <li>• Generally are used mixtures of many plants (often more than 10 together!), thought synergic. Products often do not contain any reference to the chemical constituents nor extraction technique.</li> <li>• Generally believed safe and without any adverse reaction.</li> <li>• Pathogenesis of illnesses and therapy are often based on philosophic, religious and socio-cultural conception, and are referred to the character and emotions of a patient (holism).</li> </ul>	<ul style="list-style-type: none"> <li>• Use of proper extractive and pharmaceuticals preparation of plants.</li> <li>• Generally used purified and standardized in the chemical constituents that have a pharmacological activity, and are used as symptomatic, for prevention or treatment.</li> <li>• Possible side effects, contraindications, drugs interactions, etc.</li> <li>• Diagnostic and therapeutic methodology follows the rules of mainstream medicine, because the reference for clinical administration is only the pharmacological activity based on conventional laboratory techniques and clinical trials.</li> </ul>

years or just months after migration a TMS can have absorbed cultural influences from the host country (3).

### Efficacy and Effectiveness of a Traditional Herbal Remedy

To evaluate the efficacy, effectiveness and safety of a traditional herbal remedy requires answers to some basic questions:

- (i) Which treatment should be studied?
- (ii) Can it be studied following the patterns of modern science protocols?
- (iii) Is it scientifically correct to transfer a remedy directly in another country?
- (iv) Does already exist a conventional treatment safe and effective?
- (v) Is ethically correct to study that type of remedy?

Several factors are important in determining the outcome of any traditional treatment, both in experimental and clinical settings including *forma mentis*, beliefs, knowledge and practical abilities of the provider, as well as the positive or negative prejudices of the patient with respect to the provider of the therapy, cultural differences in the acceptability of the treatment and adherence to it, the patient-doctor encounter, and differences in access to other treatments (4). In the age of globalization and of the so-called 'plate world', assessing the 'transferability' of treatments in herbal medicines is not a relevant goal for clinical research, while efficacy and safety should be based on the normal patterns of mainstream clinical medicine. The CONSORT statement for trials of herbal medicines (5) can be a very important paradigm to follow; and in fact it elaborated 9 of the 22 CONSORT checklist items to enhance their relevance to trials of

**Table 2.** European medicinal plants from traditional uses to scientific knowledge

Medicinal plant	Traditional uses	Scientific knowledge
Bergamot ( <i>Citrus bergamia</i> )	Fragrances, disinfectant, healer	Photosensitizer, Mutagen-cancerous
Chaste tree ( <i>Vitex Agnus castus</i> L.)	Anxiety, convalescence sexual sedative	Premenstrual syndrome
Coltsfoot ( <i>Tussilago fanfara</i> L.)	Cough sedative	Hepatotoxic and Mutagenic alkaloids
Garlic ( <i>Allium sativum</i> L.)	Influenza and diarrhea, aphrodisiac and abortive. Used against parasites and witches	Platelet antiaggregant. Hypolipidemic and hypotensive herbal remedy
Greater celandine ( <i>Chelidonium majus</i> )	Hepatobiliary diseases (yellow latex for yellow bile)	Hepatotoxic
Germander ( <i>Teucrium chamaedrys</i> L.)	Depurative, digestive, slimming	Hepatotoxic
Marigold ( <i>Calendula officinalis</i> L.)	Hemmenagogus, liver depurative gastric ulcer, dysmenorrhea	Hemollient and healer (only topic use)
St Jhon's wort ( <i>Hypericum perforatum</i> L.)	Burns, gastritis, magical uses	Antidepressant, Induction of CYP3A

herbal interventions, including minor recommendations for eight items. Besides, Nahin and Straus from the National Center of Complementary and Alternative Medicine (NCCAM) proposed a pragmatic schema for allocation of resources in the USA. The authors recommend five criteria: quantity and quality of available preliminary data to help determine the most appropriate type of research; extent of use by the public; public health importance of the disease being treated; feasibility of conducting the research; cost of the research (6).

It is very important to keep in mind the differences between explanatory and pragmatic studies, and the concepts of efficacy and effectiveness (7); efficacy is the benefit a treatment produces under ideal conditions, often using carefully defined subjects, while effectiveness defines the benefit the treatment produces in routine clinical practice (8). Explanatory trials evaluate the efficacy of a treatment under controlled conditions that optimize isolation of the treatment effect through design features, such as a control or placebo, randomization, standardized protocols, homogeneous samples, blindness; these type of studies often represent the treatment of a particular patient, that is not the usual patient that enter a medical office. Pragmatic studies do not provide conclusive information on the specificity of the treatment effect but they have some interesting characteristics.

### Pragmatic studies in Traditional Medicine

Pragmatic trials (PT) are designed to find out about how effective a treatment actually is in everyday practice; while explanatory trials are designed to find out whether a treatment has any efficacy, almost always compared with placebo under ideal conditions. PT answers questions about

the overall effectiveness of an intervention, and cannot study the contributions of its different components. The participant to these studies will need to be representative of the wider population because results need to be generalized; so wide criteria of inclusion are needed, so that patients having more medical diseases or taking different medications are included. It would be more satisfactory and sensible to choose conditions where conventional treatment is often unsatisfactory like irritable bowel syndrome or panic crises. In PT it is not usually mandatory to use a placebo, while it is needed with both arms of the trial on normal practice, since the aim is to produce an evidence to facilitate a real practical choice. The treatment protocol is more complex because patients with wider criteria are included, so is necessary a larger sample of patients, and may need a handbook that defines parameters for treatment (9). The main advantage of PT is that they can deliver evidence of effectiveness directly in clinical practice (10). Nevertheless they have important methodological limits: most of all the lack of placebo and blindness, increased costs, the need of several therapists, more complexity and lack of clarification about the mechanism of action; but PT should be seen not as an alternative to explanatory studies, but as a mandatory complement that define and improve evidence primarily coming from explanatory trials, the only one that can reliably confirm efficacy.

### The Chemical Constituents of Herbal Remedies

The other black box of herbal-based treatments is the lack of information about the composition of the remedy. Herbs are natural products and their chemical composition varies depending on several factors, such as botanical species, used chemotypes, the anatomical part

of the plant used (seed, flower, root, leaf, and so on) and also storage, sun, humidity, type of ground, time of harvest, geographic area; and merchandized products containing on the label the same product varying in their content and concentrations of chemical constituents from batch to batch; and even the same manufacturer can merchandize in different periods products containing different substances although standardized to achieve a high pharmaceutical quality. This variability can result in significant differences in pharmacological activity: involving both pharmacodynamic and pharmacokinetic issues.

Adverse and side effects is another open problem, because in citizens still prevail the respect for everything that is natural tout court, more as a cultural-fashion-based choice than thinking that the patient is introducing in his/her body chemical substances of vegetal origin; not knowing that salicylic glucosides and lactonic sesquiterpenes of many Compositae are often responsible of allergic reactions; that some constituents of plants are cancerogenic like safrole, bergapten and pyrrolizidines alkaloids. Not of minor importance especially for the old patient using contemporary more synthetic drugs is the problem of drug interferences; some plants reduce or improve the bioavailability of some drugs due to induction or inhibition of cytochromes (St. John's Wort extracts, grapefruit juice, and so on). Moreover the use of herbal extracts during pregnancy or lactation should undergo strict medical supervision because many herbs have not been studied neither in pregnant mice.

Advances in high-throughput experimentations have resulted in massive databases of genomic, proteomic and chemical data which in combination with efficient separation methods and powerful spectrometric methods for identification and structure elucidation can be used for identification of active compounds (11). A powerful and deep biological approach that integrates such large and diverse sources of information together actually needs to fully understand the pharmacological effects of natural products; and DNA microarrays may provide a suitable high-throughput platform for research and development of drugs from natural products (11). There are three main applications of DNA microarrays: in pharmacodynamics for discovery of new drugs; in pharmacogenomics for prediction of side-effects; in pharmacognosy for correct botanical identification and authentication of crude plant materials as part of standardization and quality control (11).

## Conclusions

Herbal-derived remedies need a powerful and deep assessment of their pharmacological qualities and safety issues due to the large and growing use of natural-derived substances all over the world, which cannot rely only on the tradition or supposed millenarian beliefs; explanatory and pragmatic studies are useful and complementary in the acquisition of reliable data both for health caregiver and patients

Evidence-based medicine (EBM) was first conceived by Archibald Cochrane as a cultural and methodological approach to clinical practice to make decisions; based on clinical expertise and the most intimate knowledge of the individual patient's clinical situations, it de-emphasizes unsystematic clinical experience as ground for medical decision-making, and stresses the rigorous analysis of evidence from clinical research. An important problematic of EBM is the difficulty to be easily applied in everyday practice, in a ABC system, especially in the field of complementary medicine, and probably pragmatic studies can be a useful tool in reaching this major objective as part of the systematic process of knowledge.

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