Phytomedicine Research in Germany

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In Germany since 1980, more than 300 clinical studies have been carried out with standardized phytopharmaceuticals, including Crataegus, Silybum, Ginkgo, Hypericum, Sabal, Urtica, Kava-Kava, Allium sativum, Valeriana, Aesculus, Echinacea, and Viscum drugs. These studies assessed the efficacy of phytopharmaceuticals for the treatment of moderate or moderately severe diseases and prevention. Several comparative clinical trials showed that these phytopharmaceuticals had full therapeutic equivalence with chemotherapeutics and had the simultaneous advantage of being devoid of any adverse effects. The mechanism of action of herbal drugs and their extract preparations, which differ in many respects from that of synthetic drugs or mono substances, can be characterized as a polyvalent action and interpreted as additive or, in some cases, potentiating. Currently, a rationale for the observed reversal effects and optimal effects with very low doses after a long-term application has not been developed, but is under investigation by systematic research at the molecular level. Key words: Germany, phytomedicine research, phytopharmacology, quality proof of phytopharmaceuticals. *Environ Health Perspect* 107:779-781 (1999). [Online 25 August 1999]

http://ehpnet1.nih.gov/docs/1999/107p779-781wagner/abstract.html

In Germany, there are two reasons phytopharmaceuticals are of high standard and are classified primarily as conventional drugs by law. One reason is that during the last 50 years traditional medicine has been kept alive by both medical practitioners and the increasing interest of patients in herbal drugs. The other reason is that shortly after World War II the pharmaceutical industry specialized in and relied on herbal drugs and also developed and supported projects aimed at optimizing the quality of herbal drugs by standardization and scientific basic research. This development was paralleled by an intensified evaluation of herbal drugs and a search for the active principles of phytorepreparations.

The fight for the acceptance and registration of phytopharmaceuticals as drugs has been successful. Today in Germany most of the herbal drugs, even mixtures of herbal drugs, are registered as conventional drugs (1); this means that they meet the same stringent criteria of quality, efficacy, and safety as synthetic drugs. These requirements of the German drug law has stimulated the search for the active principles in medicinal plants and phytorepreparations, the development of standardization methods of phytorepreparations, and the performance of clinical trials.

The search for the active principles was an important prerequisite for the standardization procedure. In contrast to investigations carried out 10 or 20 years ago, most extract fractionations were performed using bioguided methods and the diode array high-performance liquid chromatography (HPLC) technique (2,3). These techniques may be quickly performed and allow researchers to focus on those fractions or compounds that are expected to be responsible for the pharmacologic activity of an herbal drug. Because of the use of new target models in pharmacology, there has been remarkable progress in determining the mechanisms of action and the true active constituents of herbal drugs. For example, the well-known antitumor activity of garlic derives partly or totally from apoptosis induced by reactive oxygen species via the transcription nuclear factor kB of the tumor cell (4). In another experiment, Dirsch et al. (3) revealed that alllicin and ajoene, the major constituents of fermented garlic extracts, inhibit the nitric oxide-synthase of macrophages and, by this, the generation of NO species, which in turn may be involved in the pathophysiology of atherosclerosis. In a new approach to elucidate the antiprostatic active principle of the roots of *Urta dioica* (stinging nettle) root, we showed that one major constituent in the water extract of this herbal drug, the *Urta* lectin UDA (*Urta dioica* agglutinin), binds to the epidermal growth factor receptor of the prostate cell and thus inhibits prostate growth (6).

Further insights into the mechanisms of action of herbal drugs have been obtained by novel bioguided phytochemical investigations with *Echinacea*, *Hypericum*, and *Crataegus* drugs (7–9). In many cases, the overall pharmacologic effects and therapeutic efficacies derived not from a single compound but from several compounds generating additive or synergistic pharmacologic effects. This means that the standardization method to be applied should include at least two or more compounds according to methods established by the national pharmacopoeias or additional specific herbal drug monographs. Because the criteria for the quality proof of an herbal drug differ from country to country, steps should be taken toward a global harmonization of the guidelines, e.g., by the International Federation of Pharmaceutical Manufacturers Association (IFPMA), which represents the global research-based pharmaceutical industry and aims to ensure the same standards of safety, quality, and efficacy for new medicines and more efficient registration for use worldwide. These endeavors are handicapped when the active principles are only partly known or when a mixed preparation contains several raw drugs or extracts. In this case, a fingerprint chromatogram of the extract or preparation obtained by HPLC, gas chromatography (GC), or thin-layer chromatography (TLC) is the most appropriate way to document the quality (3). This fingerprint should demonstrate identity and purity of a drug and should guarantee the therapeutic equivalence of extracts from the same herbal drug. Single marked constituents can be quantified. An exact chemical characterization of all major constituents of an extract can only be achieved by specific and selective analytical methods such as HPLC with diode array detection, HPLC-mass spectrometry, or capillary GC with mass detector. If a phytoreparation contains more than four or five drugs or extracts, it is more reliable to characterize the individual drugs or extracts by HPLC before mixing them. For publication and registration of phytotherapies in Germany, it is mandatory that pharmacologic experiments be performed with at least two or three batches of the phytoreparation from different time periods to confirm reproducible processing and to guarantee stability and the same efficacy of the preparation.

Before initiating a clinical trial, all toxicity studies necessary to establish the safety of the trial must be performed. From 1970 to 1985, the first phase of herbal drug investigations in Germany was completed; this involved proving quality of these phytotherapies and a thorough search for the various active principles. This phase was followed by clinical trials that initially focused on about 10 herbal drugs or phytorepreparations which were already on the market, but for which sufficient good clinical practice studies were lacking.

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Received 14 January 1999; accepted 8 July 1999.
The herbal drugs include:
- Hawthorn leaf with flower (*Crataegus monogyna, C. laevigata*).
- Garlic (*Allium sativum*).
- Ginkgo biloba leaf.
- St. John's wort herb (*Hypericum perforatum*).
- Valeriana root (*Valeriana officinalis*).
- Echinacea purpurea herb.
- Kava-Kava root (*Piper methysticum*).
- Milk thistle fruit (*Silybum marianum*).
- Saw palmetto fruit (*Serenoa repens*).
- Nettle root (*Urtica dioica*).

One of the first clinical trials was performed with hawthorn extract (*Crataegus sp.*), which was standardized on flavonoids and procyanidins. It has been suggested that both classes of compounds are the major active principles and are involved in the positive inotropic and coronary artery-dilating effect described for *Crataegus* extract (10,11). Meanwhile, an angiotensin-I-converting enzyme (ACE) inhibiting effect could be demonstrated for the oligomeric procyanidins (12). The results of the trials were accepted by the German Drug Administration for the treatment of nondigitals-dependent patients with heart insufficiency stage I and II according to the New York Heart Association. In a double-blind study of the standardized *Crataegus* extract and captopril, the mean score values of complaints recorded after 8 weeks of treatment showed the same degree of improvement in both groups (13).

Other trials were performed with the same positive results, e.g., with standardized Ginkgo, *Hypericum* (St. John's wort), Kava-Kava, Sabal, *Urtica*, and *Echinacea* preparations (1). Fourty-four double-blind studies indicate the efficacy of various Ginkgo extracts for the treatment of cognitive disorders. Kleijnen and Knipschild (14) described eight of these studies and determined that they were performed correctly and without methodologic shortcomings. A recently published double-blind study performed with a Ginkgo extract showed promising results when the extract was applied for the treatment of dementia and, in particular, for Alzheimer disease (15).

The *Hypericum* extract, which is now widely used for the treatment of moderate and less severe depression, was investigated in several placebo-controlled double-blind studies (16). Some of these studies were also performed in parallel with the synthetic psychopharmaceuticals imipramine and maprotiline (17). Surprisingly, a 6-week treatment with *Hypericum* extract with one of the synthetic drugs in parallel resulted in the same significant reduction of the Hamilton Depression Anxiety (HAMDA) score values, with the advantage that there were no side effects with the *Hypericum* medication (17).

Another accepted use of herbal drugs is for the treatment of benign prostatic hyperplasia. Germans spend approximately 250 million deutsche marks (wholesale price) per year on prostate remedies, whereas in the United States, surgical treatment is the gold standard in urology. In Germany, many urologists believe that treatment should not target primarily benign prostatic hyperplasia as such, but only the associated symptoms, especially the distressing symptoms of obstructive and irritative urination (1). In the last 10 years, many clinical and pharmacologic studies have confirmed the observations made when extracts of *Urtica* root, *Serenoa repens* fruits (saw palmetto), *Cucurbita pepo* (pumpkin) seeds, and *Hypoxis rooperi* were used to treat prostate symptoms (1). The Sabal, *Cucurbita*, and *Hypoxis* drugs; sterins; and other lipids have been suggested to be responsible for the antiinflammatory and cell proliferation-inhibiting effect of the extracts. Similar positive effects observed with *Urtica* extracts may be caused by a synergism of polar compounds such as UDA and polysaccharides (18). In recent years, *Echinacea* preparations have developed into the best selling herbal immunostimulants for the adjuvant therapy of recurrent infections of the respiratory and urinary tracts and for the prevention and therapy of common colds and flu (19). Thorough phytochemical investigations have revealed chirc acid, alkylamines, and polysaccharides to be the putative major active principles responsible for the enhancement effect on the unspecific immune system (7). Six clinical studies performed with *Echinacea* preparations, reviewed by a meta-analysis, have confirmed the therapeutic efficacy, but further investigations are necessary to find the optimal dosage and application form (20). The list of herbal drugs that have been intensively investigated in the last 10 years by phytochemists, pharmacologists, and clinicians includes *Silybum marianum* (milk thistle), *Allium sativum* (garlic), *Vicia album* (mistleoe), *Piper methysticum* (Kava-Kava), *Harpagophytum procumbens*, *Aesculus hippocastanum* (horse chestnut), and *Valeriana officinalis*. Clinical studies have been performed for these phytopreparations (1). The other than the clinical proof of efficacy, several new scientific findings have arisen from the many pharmacologic and clinical investigations that have been performed with the various phytopreparations. They provide insight to the mechanism of action of herbal drugs, which in many respects differs from that of synthetic drugs. The new findings can be summarized as follows:

- Phytopreparations are applicable primarily for the treatment of moderate or moderately severe diseases. This limitation is often designated "for stage I and II" of any disease. In addition phytopreparations can also be used as adjuvants in combination with a strongly acting chemosynthetic drug.
- The positive clinical results obtained with phytopreparations fully justify this type of classification.
- As shown in several comparative clinical trials (21), several phytopreparations that were selected according to the above criteria showed full therapeutic equivalence with chemotherapeutics and had no adverse effects.
- If one compares the concentrations of the active compounds of an herbal drug with those of a strongly acting chemotherapeutic drug, it is evident that most phytopreparations exert their effects at much lower concentration. The ratio can be 1:1 or more. This difference can be explained by potentiating synergistic effects caused by the various compounds in a raw herbal drug or extract when no interactions between the several compounds are likely or when interactions can be excluded on the basis of pharmacologic experiments. The measurement of synergistic effects can be made with a two-component mixture of substances according to the isobol method of Berenbaum (22), but it is not applicable for herbal extracts. Therefore, an indirect method using the results of clinical trials can be used: for example, if 1 g of a plant extract containing a total amount of 1% bioactive compounds (approximately 10 mg) is found to be therapeutically equivalent to approximately 100 mg of a synthetic substance at a given equal indication (as evidenced in a clinical trial), the bioactive compounds of the extract may possess polyvalent activities and exhibit a synergistic (potentiating or overadditive) pharmacologic effect. This conclusion is justified if the single components of the bioactive compounds alone have very low pharmacologic activities. Furthermore, it must be concluded that the activities of the single components are directed against different pharmacologic targets. In this context, it should not be assumed that a 5- to 10-fold potentiation of an overall pharmacologic effect is caused only by an increased solubility and by the enhanced oral uptake of the compounds of the extract by the gut.
- Another phenomenon observed for many phytopreparations is dose-dependent pharmacologic or therapeutic reversal effects if the same preparations are applied at high and very low doses. For example, the cytostatically acting vincristine, which is usually applied in vivo in milligram concentrations, can activate the nonspecific immune system in minute (microgram or nanogram) quantities (23).
- Many phytopreparations exhibit no immediate pharmacologic or therapeutic effects and achieve their optimal efficacy only
after long-term treatment. This effect has been demonstrated in an in vivo study with a Crataegus extract, which resulted in an increase in myocardial blood circulation only after a 3-week application (24). These new findings need a scientific explanation, especially where the mechanisms of action and possible interactions are concerned. There is a general consensus that these described phenomena, which at present have no rationale, must be elucidated by thorough and systematic research at a molecular level.

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