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Reports

Report on the 3rd International ESCOP-Symposium

The third International Symposium of ESCOP (European Scientific Cooperative on Phytotherapy) on medicinal plants at the Hague-Scheveningen, The Netherlands, on March 18th, was attended by over 200 delegates from 19 countries. Under the heading of the symposium "Research and Therapy with Phytomedicines" speakers from Germany, Ireland, The Netherlands and the United Kingdom adressed issues of research and clinical practise with phytomedicines.

In his welcome adress the president of the Dutch Society of Phytotherapy, Professor Dr. R. P. Labadie (Univ. Utrecht, the Netherlands) mentioned that the promotion of both research and of good therapy with phytomedicines is central to ESCOP's objectives. To achieve such goals and objectives scientific evaluation and verification of medicinal and medical knowledge is the primary requirement. Experimental testing and clinical trials consequently follow literature and field work investigations. Clear cut advances in methodological approaches were made in the last fifteen years to handle such complex nature of phytomedicinal preparations. By means of activity-guided experimental techniques major results have been achieved. Such work leads to the identification of biologically and pharmacologically active constituents. The discovery of new mechanisms of action through these investigations opens perspectives for new approaches in therapy. So research on phytomedicines does contribute to novel drug developements. The possibilities and the potential given by medicinal plants with their secondary metabolism and metabolites are of major importance as a starting point to use plants as resources for the developement of drugs and in particular of phytomedicines.

In his general overview "Facts, Methods, Results and Progress" Dr. D. Corrigan (Dept. of Pharmacognosy, Trinity College, Univ. of Dublin, Ireland) stated, that phytotherapy can be envisaged as including three interdependent components, namely the patient, the phytomedicine(s) and the practitioner. A review of the state of knowledge about these key elements shows that while data on the phytomedicines and on the patients using them are already extensive and increasing in volume and in sophistication, information about the role of phytotherapy practitioners, their expectations and needs may not be optimal. Phytomedicines have a major role to play as integral elements of modern health care systems, which, due to public demand, requires the integration not only of medicinal agents of diverse origin (synthetic, biotechnological and botanical) but also an integration of different therapeutic modalities. Recent work by the ESCOP Scientific Committee within the SPC (Summary of Product Characteristics) framework, on an extensive range of medicinal plants, highlights both the advances made to date and also the constraints which must be resolved by those at the forefront of phytotherapy practise and research on the one hand and by those charged with medicines regulation on the other. The clarification of these unresolved issues has major implications for the leadership role of ESCOP in the field of phytotherapy.

The pioneering work of ESCOP in drawing together phytomedical expertise from around Europe has now received endorsement by the European Commission. S. Y. Mills (Univ. of Exeter, Centre for Complementary Health Studies, Exeter, United Kongdom) reported on the grant given by the EU Biomedical and Health Research Programme (BIOMED 1) for a multi-centre research project to determine "European standards for the safe and effective use of phytomedicines".

The project supports ESCOP's existing work in preparing proposals (SPCs) to be submitted to the European CPMP (Committee for Propreitary Medicinal Products) for those herbs used in licenced phytomedicines. Besides SPC-Production the funding is also stretched to support work on the evaluation of safety and efficacy. This work includes setting up a pilot pharmacovigilance project as well as an expert panel with expertise in appropriate research methodologies. The first will involve new attempts to determine the level of adverse effects of taking phytomedicines against the background or other national adverse drug reaction reporting schemes for medicines as a whole. The final part of the project will be concerned with improving standards of efficacy. Following a consultation exercise started by the Research Committee of ESCOP this proposal will involve further clinicians, clinical pharmacologists and biometricans and other researchers already active in producing clinical data, with the prospect of setting up a standing committee providing peer reviews, methodological and ethical advice, and a support network for research facilities.

Dr. K. Keller (Bundesgesundheitsamt Berlin, Germany) presented facts and figures, concerning phytotherapy on the European level. He pointed at the fact that herbal remedies are medicinal products and therefore fall within the scope of Council Directive 65/65/EEC. As such, quality sa-

fety and efficacy must be demonstrated. The criteria of quality assessment of herbal remedies are documented in the EEC Note for Guidance "Quality of Herbal Remedies". In demonstrating safety and efficacy, it is open to an applicant to refer to "bibliographic data", in accordance with Article 4 No. 8a (ii) of CD 65/65/EEC. Herbal medicinal products are a relevant factor in harmonization due to their number and due to their economic relevance. They are used in all Member States of the EEC. As is true for all substances of biological origin, the definition of a herbal drug preparation must take into account the different botanical sources and the processing of the herbal drug. A harmonization of medical assessments of herbal Pharmacopoeia is therefore an indispensable basis for any concerted decision. The Bundesgesundheitsamt (BGA) has been asked in March 1991 by the CPMP to act as a rapporteur in summarizing the status of herbal remedies evaluation within the EEC. An inquiry made in the Member States in 1991, gave the impressive number of about 1400 herbal drugs used in the EEC. When the BGA focused on those drugs which were used in half of the responding Member States (5 out of 10), still 145 herbal drugs were documented. Keller concluded by saying: "My personal summary of experiences gained within the last years in discussions on the herbal remedies is a positive one. Herbal remedies were discussed in the CPMP open mindedly and constructively. All Member States were highly interested to find solutions to the questions raised. This was possible because the difficult subject was presented by ESCOP on a high scientific level. As we know from earlier years, a discussion on herbal remedies would probably not have reached any concrete results without the activity of ESCOP. As a rapporteur I should like to thank ESCOP for the good quality of the revised documents. Future activities will depend on the priorities set by the EEC Commission in the harmonisation of new and old products, of OTC and of herbal products, and on the personal and last but not least financial resources of CPMP. My personal position in these competing priorities is that there is no reason why OTC and herbal medicinal products should not circulate freely in the common market and harmonisation should be a priority in all cases where divergence is considerable".

Referring to toxicological aspects of phytomedicines Dr. Hilke Winterhoff (Inst. of Pharmacology and Toxicology, Univ. of Münster, Germany) drew the attention to the fact that as toxic effects are common with therapeutically used chemical substances, they can also be seen with phytomedicines. Therefore the evaluation of toxic risks is important for further improvement of drug safety. Several side effects of herbal products are not to be attributed to the use of phytomedicines in general. So avoidable risks may result from using starting material of inferior quality, from inadequate drug processing or by inappropriate use of the phytomedicine.

Toxic effects of phytomedicines can also occur with drugs of proven efficacy and satisfying pharmaceutical quality. An example for such a drug is Glycyrrhiza glabra. Extracts from the roots proved to exert secretolytic and spasmolytic effects, and in addition an anti-ulcer activity was established. Higher doses as well as long term use caused an indirect mineralcorticoid effect with sodium retention, edema, hypertension and hypokalemia. These effects result from a change in the intrarenal cortisol metabolism caused by glycyrrhetic acid, the active metabolite of glycyrrhicic acid. This toxic effect can be avoided by removing the constituent responsible for the adverse effect, glycyrrhicic acid, which is not the biologically active compound. The same is true for pyrrolizidine alkaloids containing drugs, in which a reduction of the PA content is irrelevant for their pharmacological effects.

But not in any case toxic effects can be avoided such as gastrointestinal complaints which are reported more frequently or allergic reactions, which occur independently of the dose of the drug applied. In no respect even a grave allergic reaction does justify limitations of the use of such a plant, whereas a label for the user of a special allergic risk seems to be essential. Thus for instance Arachis hypogea can cause severe systemic allergic reactions, but nobody could take this as a reason to limit by law the use of peanuts.

It is assumed and generally accepted for herbal drugs with a long traditional use in Europe that direct toxic risks of these plants can be ignored. Their low toxicity even after overdosage was stated repeatedly. On the contrary mutagenic and cancerogenic risks can not be excluded even for drugs with a long traditional use. A moderate or slight increase in tumor incidence would not be detected at all.

Prof. Dr. B. Schneider (Univ. of Hannover, Institute of Biometry, Hannover, Germany) reported on biometric methods with special reference to the assessment of the efficacy of phytomedicines. The established method for the assessment of the therapeutical efficacy of drugs is the controlled clinical trial, the experimental principle of which was established during the 17th to 19th century. The leading concepts behind this principle are objectivity, causality and universality. Assessment of the therapeutical efficacy is performed by comparison of the drug effect with the effects achieved with other drugs or without drugs. For establishment of the universality of the drug effect statistical methods are necessary.

These principles are generally valid for the assessment of therapeutic efficacy and also phytomedicines are bound to these principles. Special problems arise from special applications. Application of phytomedicines is often concerned with a broader pattern of symptoms and more individual changes of health states. Another problem is the inclusion of past experience (historical data) in the assessment of therapeutic efficacy, for the handling of which special procedures are necessary.

The lectures of Dr. H. van Dijk (Academic Hospital Ut-

recht, Lab. for Microbiology, Utrecht, Niederlande) on "Phytomedicines and the immune system", Prof. Dr. D. Loew (University Frankfurt/Main, Germany) on "Demonstrated pharmacological and clinical results with Crataegus Special Extracts in cardiac insufficiency", Dr. H. F. Dankmeijer (Diabetes Center Bilthoven, Niederlande) on "Phytotherapeutical aspects of diabetes" and Prof. Dr. J. David Phillipson (Dept. of Pharmacognosy, School of Pharmacy, Univ. of London, U.K) on "Traditional medicine treatment for eczema – Experience as a basis for scientific acceptance" referred to the practical use of phytomedicines.

Supporting the lectures was a poster exhibition on current research and 31 examples were submitted with the five best researchers receiving a prize of a thousend guilders and encouragement from Prof. R. P. Labadie to continue their scientific work.

ESCOP has become the leading international authority on phytotherapy with advanced scientific programmes dealing with quality, efficacy and pharmacovigilance of phytomedicines. To this end a RESOLUTION was acclaimed by members of the participating countries as well as by the representatives of Scientific Associations for Phytotherapy from nineteen countries which reads as follows:

1. ESCOP stimulates scientific research into safety and efficacy of phytomedicines by means of the Biomedical and Health Research Programme of the European Union. This programme contains the developement of European standards for safety and efficacy of phytomedicines. Within this framework of research, the complex nature of phytomedicines is taken into account.
2. ESCOP offers well-considered and scientifically based expertise and information concerning phytomedicines. In the interest of public safety ESCOP has a comprehensive pharmacovigilance programme to monitor the use of phytomedicines and provide accurate information to regulatory authorities, the media and general public.
3. ESCOP supports clinical research with phytomedicines. Within this research the results with the used and characterized phytomedicines should be applicable to comparable preparations.
4. ESCOP is of the opinion that the treatment by means of phytomedicines should continue to be a part of national health care systems in Europe.
5. ESCOP has been working on European criteria for the assessment of phytomedicines in order to assist the promotion of harmonization process since 1989. To this end ESCOP monographs have been published and submitted to the CPMP.

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Table 1: Drugs in the EU (K. Keller 1994).

Achillea millefolium	Herba	Barosma betulina	Folium
Acorus calamus	Rhizoma	Betula pendula	Folium
Aesculus hippocastanum	Semen	Calendula officinalis	Flores
Agar		Capsella bursa-pastoris	Herba
Agrimonia eupatoria	Herba	Capsicum annuum	Fructus
Agrimonia procera	Herba	Carum carvi	Fructus
Agropyron repens	Rhizoma	Cassia angustifolia	Folium
Alchemilla vulgaris	Herba	Cassia senna	Folium, Fructus
Allium cepa	Bulbus	Centaurium erythraea	Herba
Allium sativum	Bulbus	Cephaelis ipecacuanha	Radix
Aloe species (barbadensis,		Chamomilla recutica	Flores
capensis, ferox)	Succus (sicc.)	Chondrus crispus	Thallus
Alpinia officinarum	Rhizoma	Cimicifuga racemosa	Rhizoma
Althaea officinalis	Flores	Cinnamomum aromaticum	Cortex
Althaea officinalis	Folium	Citrus limonum	Aetheroleum
Althaea officinalis	Radix	Cnicus benedictus	Herba
Anethum graveolens	Fructus	Cola nitida	Semen
Angelica archangelica	Radix	Commiphora molmol	Gum-Resin
Arctium lappa	Radix	Coriandrum sativum	Fructus
Arctostaphylos uva-ursi	Folium	Crataegus laevigata	Folium
Armoracia rusticana	Radix	Crocus sativus	Stigma
Arnica montana	Flores	Curcuma longa	Rhizoma
Artemisia absinthium	Herba	Cynara scolymus	Folium
Atropa bella-donna	Folium	Drosera rotundifolia	Herba

Equisetum arvense	Herba
Eucalyptus species	Aetheroleum
Ferula asa-foetida	Gum-Resin
Ficus carica	Fructus
Filipendula ulmaria	Flores, Herba
Foeniculum vulgare var. vulgare	Aetheroleum
Foeniculum vulgare var. vulgare	Fructus
Fraxinus excelsior	Cortex
Fraxinus excelsior	Folium
Fucus vesiculosus	Thallus
Fumaria officinalis	Herba
Geranium robertianum	Herba
Glycyrrhiza glabra	Radix
Hamamelis virginiana	Folium
Harpagophytum procumbens	Radix
Hedera helix	Folium
Humulus lupulus	Glandula
Humulus lupulus	Strobuli
Hydrastis canadensis	Rhizoma
Hypericum perforatum	Herba
Hyssopus officinalis	Herba
Illicium verum	Fructus
Inula helenium	Rhizoma
Juniperus communis	Fructus
Krameria triandra	Radix
Lamium album	Flores
Laurus nobilis	Folium
Lavandula angustifolia	Flores
Levisticum officinale	Radix
Linum usitatissimum	Semen
Lobelia inflata	Herba
Malva sylvestris	Flores
Malva sylvestris	Folium
Marrubium vulgare	Flores
Marrubium vulgare	Herba
Melaleuca species	Atheroleum
Melissa officinalis	Folium
Mentha piperita	Aetheroleum
Mentha piperita	Folium
Menyanthes trifoliata	Folium
Myristica fragrans	Semen, Arillus
Myroxylon balsamum var. pereirae	Balsamum
Olea europaea	Folium
Olea europaea	Oleum
Origanum vulgare	Herba
Panax ginseng	Radix
Papaver rhoeas	Flores
Passiflora incarnata	Planta tota
Peumus boldus	Folium
Pimpinella anisum	Fructus
Pimpinella anisum	Fructus, Aetheroleum
Pinus species	Aetheroleum (Terpentin)
Plantago ovata	Semen
Podophyllum peltatum	Rhizoma, Resina
Polygonum aviculare	Herba
Potentilla erecta	Rhizoma
Primula veris	Radix
Prunus cerasus ssp. acida	Stipites
Prunus spinosa	Flores
Quercus robur	Cortex
Quillaja saponaria	Cortex
Rhamnus frangula	Cortex
Rhamnus purshianus	Cortex
Rheum officinale	Radix
Rosa canina	Fructus
Rosa centifolia	Flores
Rosmarinus officinalis	Folium
Rubus fruticosus	Folium
Rubus idaeus	Folium
Salvia officinalis	Folium
Sambucus nigra	Flores
Silybum marianum	Fructus
Silybum marianum	Herba
Solidago virgaurea	Herba
Tamarindus indica	Fructus
Taraxacum officinale	Radix
Thymus serpyllum	Herba
Thymus vulgaris	Herba
Tilia cordata	Flores
Trigonella foenum-graecum	Semen
Urtica dioica	Radix
Vaccinium myrtillus	Folium
Valeriana officinalis	Radix
Verbascum phlomoides	Flores
Verbascum thapsus	Flores
Verbena officinalis	Herba
Viburnum prunifolium	Cortex
Viola odorata	Flores
Viola tricolor	Flores
Viola tricolor	Herba
Vitis vinifera	Folium
Zea mays	Stipites
Zingiber officinale	Rhizoma

Erratum

K. Galle et al., Phytomedicine *1*, 59–62 (1994) "Analytical and pharmacological studies on Mahonia aquifolium" (page 60, alkaloid quantification):

Instead of the given total alkaloid content of the mother tincture and of the methanol extract of the raw drug read 0,2 and 0,27% respectively.

The printed percentage values (2,0 and 2,7%) refer to the raw drug.