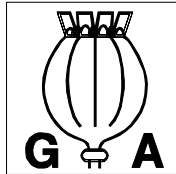


**International Symposium
of the
Society for Medicinal Plant Research**



**50 Years
„Gesellschaft für
Arzneipflanzenforschung“**

**History and Future
of Medicinal Plant Research**

Bad Camberg/Taunus – Germany

8. April 2003

Welcome address of the Mayor of the town Bad Camberg

Grußwort des Bürgermeisters der Stadt Bad Camberg

Sehr geehrter Herr Präsident,
verehrte Damen und Herren der Gesellschaft für Arzneipflanzenforschung,

im Jahr Ihres 50-jährigen Bestehens darf ich Sie in der Stadt Ihrer Gründungsversammlung, in der hessischen Kur- und Badestadt Bad Camberg, herzlich willkommen heißen und Ihrer Gesellschaft die herzlichen Glückwünsche zu Ihrem 50-jährigen Stiftungsfest übermitteln.

Aus bescheidenen Ursprüngen in der unmittelbaren Nachkriegszeit in der Kleinstadt Camberg 1953 gegründet, hat sich Ihre Gesellschaft zwischenzeitlich zu einer international angesehenen Organisation zur Förderung von Forschung und Wissenschaft auf dem Gebiet der Arzneipflanzen entwickelt. Nicht nur die alljährlich von Ihnen durchgeführten und weltweit beachteten wissenschaftlichen Tagungen, sondern auch Ihre Förderung junger Wissenschaftler, Ihre wissenschaftliche Zeitschrift „Planta Medica – Natural Products and Medicinal Plant Research“ wie auch Ihre beachtliche Mitgliederzahl in über 70 Ländern sind Ausdruck Ihrer internationalen Anerkennung und der Reputation der Gesellschaft.

Insofern freue ich mich als Bürgermeister der heutigen Kur- und Kneippstadt Bad Camberg im Taunus, Sie anlässlich Ihres 50-jährigen Stiftungsfestes an der Stätte Ihres Ursprungs herzlich willkommen zu heißen und Ihnen einen angenehmen Aufenthalt und eine wissenschaftlich anregende Tagung zu wünschen.

Die Stadt Bad Camberg ist hoch erfreut, eine so hochkarätige wissenschaftliche Tagung in Ihren Mauern willkommen zu heißen.

Mit freundlichen Grüßen

Gerhard Reitz
Bürgermeister

Dear colleagues,

50 years ago, on April 8, 1953, the „Gesellschaft für Arzneipflanzenforschung“ - GA - was founded in Bad Camberg. Originally an association of German pharmacists and medical doctors interested in medicinal plant research, GA has developed over the years into a renowned international scientific society with members from all over the world.

During these years the scientific interests of GA have broadened to all aspects of medicinally used natural products. At our annual meetings we now are regularly attracting scientists from many disciplines like agricultural science, biology, chemistry, pharmacy, pharmacognosy, pharmacology and medicine.

GA is a very active scientific society with at present more than 1000 members from 72 countries. This also reflects the global importance of medicinal plant research.

On the occasion of the 50th anniversary of GA, we have set up a symposium in which we want to look back into the history, but also into the future of natural product research. It will be a chance to meet old friends and to remember the “good old times” but also to discuss the most recent developments in medicinal plant research.

The BoD of GA has also decided to publish a book reporting the past 50 years of GA and the development of medicinal plant research during these years. We are very grateful to Prof. Sprecher, Hamburg, that he has taken over the duty of being editor in chief of this publication. The book will be presented at this meeting and will be an everlasting keepsake for this anniversary.

On behalf of GA, I would like to use this opportunity to thank all the colleagues who have supported our Society in the last five decades by offering their time and manpower; and I also want to thank our sponsors who helped that our meetings always had a solid financial basis.

I am cordially welcoming all members and friends at this historic place of the foundation of GA and wish you a pleasant day in Bad Camberg.

Prof. Dr. Rudolf Bauer
President of GA

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Guided tours (in German and English translation) through the historic heart of Bad Camberg will be offered on request at 2.30 p.m. and 5.30 p.m. Assembly point will be in front of the Kurhaus.

Programme

- 8:30** Registration
- 10:00** Opening and Welcome Addresses
R. Bauer, President of GA
G.Reitz, Mayor of Bad Camberg
F. Kemper, President of ESCOP
W. Gerwick, President of ASP
- 11:00** E. Sprecher, Hamburg
50 Years GA – The development of a scientific society
- 11:30** J.D. Phillipson, London
50 Years of medicinal plant research – Every progress in methodology is a progress in science
- 12:00** A. Nahrstedt, Münster
50 Years with Planta Medica
- 12:15** Lunch break
- 14:00** G. Franz, Regensburg
The future of herbal medicinal products from an European perspective
- 14:30** D. Melchart, Munich
Clinical effectiveness and efficacy of herbal medicinal products
- 15:00** J. Pezzuto, West Lafayette
Novel pharmacological targets for medicinal plant research
- 15:30** Coffee break
- 16:00** M. Psiorz, Ingelheim
The contribution of natural products to drug development
- 16:30** T.M. Kutchan, Halle
Genomics, proteomics and metabolomics in medicinal plant research
- 17:00** Closing

Abstracts

50 years GA – The development of a scientific society

Ewald Sprecher, Hamburg, Germany

The Founding Meeting of the Gesellschaft für Arzneipflanzenforschung (GA) - Society for Medicinal Plant Research took place at Bad Camberg (near Frankfurt/Main) on April 7-9, 1953. Beginning as a German and very soon as a German speaking Central European Society, the GA developed after a few years already into an International scientific community, at first only occasionally and then – since the 2nd half of the eighties – generally as an English speaking Society.

Between 1953 and 1958 the society's name was "German Society for Medicinal Plant Research and Therapy", between 1959 and 1969 it was called "German Society for Medicinal Plant Research" and since 1969 Society for Medicinal Plant Research.. Regardless of the changes of names the goal set has always been to unite all individuals and groups interested in medicinal plants, either in research, therapy, production or breeding and cultivation of medicinal plants. According to the bylaws, the only and immediate purpose of the society is the advancement of research in the field of and therapy with medicinal plants.

At the beginning, the founders of the GA intended to provide scientists in all fields of medicinal plant research, including therapy, a meeting place for the exchange of experiences and promotion of joint efforts. For various reasons, however, soon mainly those scientists were attracted who specialized in phytochemistry, while interests of other fields decreased. The activities of the Society emphasized in its first 20 to 30 years above all on secondary plant metabolism studying biogenesis and working on isolation and structure elucidation of secondary metabolites including quality control of medicinal plants and plant products. In the last ten years biological and pharmacological screening and clinical studies rank equally with phytochemistry. With the improvement and the refinement of analytical, biochemical and genetic tools and methods scientists introduced more and more sophisticated methods into their analytical and metabolic studies, not only with plants but also with fungi, bacteria, and certain animals including marine resources.

In the early nineties some important fields of science such as agriculture, breeding, manufacturing, quality control, and pharmacology of medicinal plants and plant products as well as regulatory affairs on herbal medicinal products, which up to then partly had been neglected, were emphasized by forming corresponding Permanent Committees.

The development of all these activities have brought about also some new aspects of modern medicinal plant research, including microbiology, biotechnology, gene technology, molecular biology and marine natural products.

Today the Society has more than 1000 members coming from 70 countries all over the world. Its scientific journal *Planta Medica* covers the whole range of medicinal plant research and has the highest Impact Factor of all journals in the field.

To recognize and promote young scientists with an exceptional doctors thesis resp. an outstanding post doc work, they can be awarded the Egon Stahl Award with bronze resp. silver medal and a monetary price. Outstanding scientific lifetime work can be awarded with the Egon Stahl Award with gold medal and also a monetary price.

50 Years of medicinal plant research – every progress in methodology is a progress in science

J. David Phillipson, London, U.K.

The participants of the first GA meeting in 1953 could not have envisaged the scientific advances that would take place in medicinal plant research in the ensuing 50 years. Chromatographic (e.g. TLC, GLC, HPLC) and spectroscopic (e.g. UV, IR, MS, ¹H- and ¹³C-NMR) techniques have had a tremendous impact on the investigation of the constituents of medicinal plants (1). Coupling of these two techniques (e.g. GC-MS, LC-MS, LC-UV, LC-NMR) has provided even more finesse and sensitivity to such investigations. In the past two decades, a series of biological assays, mainly based on specific enzymes or receptors, has been developed and utilized for medicinal plant research. As these biological techniques have progressed it has been possible to form a scientific understanding of many aspects of human biochemistry. Inflammatory diseases and immunomodulation, for e.g., can be used to illustrate how medicinal plant research has changed. Enzyme assays for inhibition of cyclooxygenase and 5-lipoxygenase, key intermediates in the inflammatory process, have been used to investigate anti-inflammatory natural products. Assays based on granulocyte phagocytosis, carbon clearance, lymphocyte proliferation, natural killer cells, tumour necrosis factor and complement factors have been used to investigate immunostimulating compounds from plants (2).

By utilizing bioassay-guided isolation techniques it has proved possible to provide scientific explanations for the activities of a number of plants used in herbal medicine, e.g. Echinacea as an immune stimulant (low mol. wt. polyacetylenes, high mol. wt. polysaccharides), St John's wort for mild-moderate depression (hyperforin), and Ginkgo for cognitive deficiency (ginkgolides, flavonoids) (3). The search for new drug entities from plants during the past 50 years can be exemplified by the clinical development of the anticancer drugs VLB, VCR, etoposide, teniposide, taxol and camptothecin from the NCI and associated programmes. The automated high through-put screens of the pharmaceutical industry, based on sensitive biological tests, have been used to investigate natural products for development of new drug entities, but it is believed that the majority of species of higher plant have not been studied biologically.

Industrial interest has now changed to combinatorial chemistry and to computer based molecular modelling design. However, it must not be forgotten that in 1991 over half of the top selling pharmaceuticals owed their origin to natural products (4) and that 44 % of the 520 new approved drugs in the USA between 1983 and 1994 were also related to natural products (5). In my view it is essential that organizations such as the GA should encourage scientific interest in all aspects of medicinal plant research including novel drug entities, herbal medicinal products, traditional medicine, biotechnology, and clinical investigations.

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50 Years with *Planta Medica*

Adolf Nahrstedt, Münster, Germany

In 1953, *Planta Medica* was founded by the Deutsche Gesellschaft für Arzneipflanzenforschung und –therapie as the Society's journal to "collect the publications connected with medicinal plants, to make the medical doctors familiar with the therapeutic usage of medicinal plants and to enable them to enlarge their knowledge about plant derived drugs according to the newest state of scientific research". For the first c. 30 years, Hippokrates Publisher produced the journal, followed by Thieme Publishers in the beginning of the 80ies. Starting slowly in the first years of its existence, *PLANTA MEDICA* then continuously developed to its current position as one of the leading journals on natural products and medicinal plants. Three Editors and many leading scientists as Co-editors or members of the Advisory Board, mostly from European countries, but also from abroad, gave *PLANTA MEDICA* its characteristic shape within 50 years. During this time, the journal has not only changed its outfit and appearance, but also its content. It started with more applied and technical aspects of medicinal plants and finally reached its main topic today i.e. the pharmacological aspects of phytochemically defined plant extracts and their active constituents. Some topics which were especially important in the 70ies and 80ies, e.g. plant cell cultures and their productive potency as well as isolation of plant metabolites and their structural elucidation; they still today fill many pages of every volume; analytical methods, the prerequisite of every sound science are another main area; new topics appear such as biopharmaceutical investigation in plant natural products. While at the beginning *PLANTA MEDICA* was exclusively German, it developed over an European to a fully international journal that was published from 1993 on exclusively in the English language. While in the fifties the appearance of the journal was at a low frequency of 2-4 issues per year, it was at 6 issues per year for a long time until 1999; a steadily growing number of submissions led to increase the number of issues in short steps to 12 in 2002. Today we look at a well developed, well known international scientific journal that receives important impact from the Society of Medicinal Plant Research but, vice versa, contributes to the international reputation of the Society.

The Future of Herbal Medicinal Products (HMPs) from a European Perspective

Gerhard Franz, Regensburg, Germany

In all EU-member states HMP's are existing with a different historical background, however, their actual importance and impact as therapeutic systems vary considerably. They might either be classified as licensed and registered medicines with a proven clinical effectiveness and safety data or otherwise as herbal products with only minor medicinal implication. It is still possible that a specific plant preparation in one country has the legal status as nutritional compound or as a 'dietary supplement' and in a third as a 'herbal drug' with an accepted therapeutic claim. An important step forward was done by the EMEA (London) providing clear cut definitions for HMP's in the EU including specifications for 'Herbal Drugs' and 'Herbal Drug Preparations'. Since the EMEA is responsible for the scientific evaluation of applications for an European Marketing Authorisation for Medicinal Products, this is certainly an improvement for the mutual recognition of herbal drug based medicine. One further prerequisite for the future recognition of HMP's are the now accepted guidelines on GAP (Good Agricultural Practice) and also on collection practice for starting materials of herbal origin. Further, a documentation of the appropriate quality of all HMP's at the different steps of production from cultivation (collection) to production (GMP) and to the final product must be guaranteed. All criteria concerning these important specifications are documented in the European Pharmacopoeia, which is continuously updated to the newest scientific state of knowledge. In the future, emphasis will be provided for HMPs on the purity criteria (determination of possible contaminants) and the quantification of active principles (standardisation) by highly sophisticated chromatographic procedures. Finally, as a consequence of many heterogeneous herbal extracts existing on the European market, standard monographs on herbal extracts will be the basis for acknowledged Europe-wide procedures. All these criteria should be documented for the future, to guarantee transparent, safe and efficient therapeutic systems for the benefit of the patient.

Clinical effectiveness and efficacy of herbal medicinal products

Dieter Melchart, Munich, Germany

In recent years a large number of randomized controlled trials and systematic reviews have been performed in the area of herbal medicine to assess effectiveness and efficacy. We collected the available systematic reviews to get an overview on the state of the evidence. Up to date more than 60 systematic reviews on herbal medicines have been published. Fourteen systematic reviews address the efficacy of ginkgo extracts for dementia and claudicatio intermittens. Most of these reviews found that ginkgo extracts were more effective than placebo but the size of effects was generally small. Eleven systematic reviews or meta-analyses were performed on the effects of hypericum extracts in patients with depressive disorders. There is clear evidence from trials performed in Germany, Austria and Switzerland that these extracts are more effective than placebo in mild and moderate depression and growing evidence that they are similarly effective as synthetic antidepressants. Trials from the US, UK and from France, however, have found no or only small effects in patients with major depression. A possible explanation for these discrepancies is that physicians in Germany select slightly different populations for treatment with hypericum extracts. Eight systematic reviews on garlic preparations suggest that certain extracts positively influence cardiovascular risk factors. One to three systematic reviews are available for a variety of other herbal medicines including preparations of echinacea, mistletoe, peppermint oil, aloe vera, artichoke, ginger, kava etc. Most of these reviews considered the available evidence as promising but rarely as fully conclusive. When interpreting the available systematic reviews several issues have to be kept in mind. Many include only small numbers of trials. The comparability of the extracts used in different trials is often unclear. Almost a third of all reviews have been performed by a single group (the Department of Complementary Medicine at the University of Exeter). In conclusion, there is promising evidence for a considerable number of herbal medicines but further research is needed in most cases to confirm these findings.

Novel Pharmacological Targets for Medicinal Plant Research

John M. Pezzuto, West Lafayette, USA

Although systemic drug therapy has been the mainstay of pharmaceutical care, the logic of disease prevention is overwhelming. This concept is clearly exemplified by large-scale vaccination programs that have virtually eradicated some diseases capable of afflicting humans. More recently, drug based strategies have been implemented for the reduction of serum cholesterol and the subsequent problems associated with heart disease. Bearing in mind the pandemic nature of cancer, therapeutic measures should also be aggressively set into motion for the prevention of this disease. Cancer chemoprevention is a process by which the phenomenon of carcinogenesis is inhibited by dietary components or pharmaceutical agents. A number of compounds mediate cancer chemopreventive activity in animal models and various clinical trials are currently underway, primarily with humans at high risk for developing cancer (1). Moreover, this principle has been established by the use of tamoxifen for the prevention of breast cancer.

Our efforts in this area have been predominately directed toward novel drug discovery (2). By means of a program project mechanism, we are capable of bringing discoveries from the field to the level of establishing in vivo efficacy with pure (structurally- and mechanistically-characterized) chemical entities. Plant extracts are first evaluated with a panel of in vitro bioassays (designed to monitor inhibition of the initiation, promotion or progression stages of carcinogenesis), and active leads are then evaluated in a more complicated and time-consuming assay, which employs carcinogen-treated mouse mammary glands in culture (2,3). Leads that are active in the organ culture system are fractionated, using an in vitro bioassay as a monitor, and the resulting active principles are evaluated in more advanced tumorigenesis models. Following this experimental design, approximately 3,000 plant materials have been evaluated and this has resulted in over 15,000 bioassay results. Over 100 compounds have been discovered that are active in various in vitro test systems, and many of these are active in preventing the formation of carcinogen-induced preneoplastic lesions in mouse mammary organ culture. Further, thus far we have discovered several lead compounds (4-9) that mediate considerable cancer chemopreventive activity in full-term tumorigenesis models. These leads are promising candidates for development as chemopreventive agents. Alternatively, agents of this type may be useful for treating cancer in direct or adjuvant settings (10).

As the armamentarium of cancer chemopreventive agents continues to expand, it is reasonable to create cancer chemoprevention drug formulations for utilization on a widespread basis by the general population. As with other pharmaceutical agents useful for disease prevention, a pharmacoeconomic analysis of a cancer chemopreventive formulation would need to be considered, and the composition of the formulation should improve over time (11). Nonetheless, it is apropos to aggressively explore the use of chemoprevention as a means of controlling cancer in the general population. The effect of delaying tumorigenesis beyond the lifespan of a normal human being is equivalent to curing cancer. This type of "cure" is achievable in our lifetime. (Supported by P01 CA48112 awarded by the National Cancer Institute).

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The contribution of natural products to drug development

Manfred Psiorz, Ingelheim am Rhein, Germany

In the last two centuries compounds isolated from natural sources such as plants, animals, fungi and other organisms, have been playing an important role as drugs. Since the isolation of morphine in 1805 has been achieved successfully, the interest in isolation and structure elucidation of natural products has never vanished. Its implication for drug research, however, has been changing during different decades. The ninetieth century has seen the use of natural products as drugs. In the 20th century medicinal chemists tended to see natural products as starting materials or as templates for synthetic drugs. This change was due to the necessity of getting patent protection as well as the aim to optimize the natural compound for various reasons.

All medicinal chemists in industry used results of academia to orientate themselves in search for interesting compounds. Special emphasis has been given to alkaloids and steroid glycosides as these categories of natural products showed strong biological activity. Until the eighties activity testing has been performed via tests at living animals and these tests were time limiting factor for R&D in industry. With the development of molecular biology, the identification of molecular targets and the isolation of enzymes, receptors, etc. substance testing became possible in *in vitro* models. The development in IT allowed to evaluate test results in large numbers and short time. HTS (high throughput screening) became a valued tool for drug identification.

To serve the test batteries it was necessary to have access to a large number of test compounds, ideally with a large structural variability. Today combinatorial chemistry can match the demand in the number of test compounds, the structural diversity of these, however, is rather limited. Here, libraries of natural products have been established to complement those derived via combinatorial chemistry. Libraries of natural products are limited in their number and by far the most expensive source for test compounds in the pharmaceutical industry. They have, however, attended high recognition in most R&D departments as they provide unmatched structural diversity to drug discovery programs. Latest developments try to combine natural products structural diversity with combinatorial chemistry.

Genomics, proteomics and metabolomics in medicinal plant research

Toni M. Kutschan, Halle, Germany

An essential aspect of a consideration of a future impact of the *omics* revolution on medicinal plant research involves establishing acceptable definitions of the terms *genomics*, *proteomics* and *metabolomics*. Genomics implies a global view of entire cellular machinery. It catalogs complete DNA sequences of organisms. This complete inventory of genome sequences cannot, however, readily be deciphered. A large number of genes cannot be identified by sequence alone, because they are not similar to any gene of known function. A systematic approach to the discovery of gene function is, therefore, necessary. This has become known as *functional genomics*, a type of high-throughput biochemistry to study gene function. Functional genomics requires measuring mRNA (transcriptome), proteins (proteome) and metabolites (metabolome) under well-defined conditions. This measurement of thousands of components in a cell defines the terms transcriptomics (mRNA), proteomics (proteins) and metabolomics (metabolites). These measurements provide a snapshot at a particular time point, under a particular set of conditions, of the complete transcriptional, translational and metabolic status of a cell.

These new technologies certainly are beginning to play an important role in phytochemistry and medicinal plant research. The largest impact is in the areas of functional genomics and in systems biology. Functional genomics has been defined above. Systems biology is a holistic approach that monitors all biological processes operating in an integrated system. This elucidates how pathways in a cell, organ or organism interact in networks. While functional genomics aims to define gene function, systems biology can, for example, identify the multiple effects that a drug has on an organism. Given these definitions, some thoughts on how *omics* are currently being used and could be used in the future in medicinal plant research will be presented.

Suggested Reading:

Plant Metabolomics Special Issue, *Phytochemistry* **62:6** (2003)

Recent Advances in Phytochemistry – Volume 36: Phytochemistry in the Genomics and Post-Genomics Eras. (J.T. Romeo and R.A. Dixon, eds.) Pergamon, Oxford (2002)

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