

Pharmacognosy at the Square — the past, the present and the future

This year, the Centre for Pharmacognosy and Phytotherapy celebrates the fifth anniversary of its revival of the discipline of pharmacognosy at the School of Pharmacy, University of London. This article explores the origins and development of pharmacognosy at the school, describes the research activities of staff in the centre over its first five years, and explains the relevance of this work to pharmacy and drug discovery today

In 1842, the Council of the Pharmaceutical Society of Great Britain established the UK's first school of pharmacy ("the Square") at its headquarters in Bloomsbury Square, London. Since then, pharmacognosy staff at the Square have achieved a reputation for strong research. Research interests were determined by the techniques available at the time and examples are given in Panel 1 (p553). Several of the staff before 1900 were designated FRS (Fellow of the Royal Society), the highest scientific award in the UK, and a number of them, post-1900, were awarded DSc degrees, the highest academic degree in the UK. When the last head of department, Fred Evans, became ill and then retired in 1998, only one member of the department, Elizabeth Williamson, remained and the subject survived through her energetic input.

From survival to revival

The continuing importance of plant medicines in traditional health care systems around the world, the increasing use of complementary and alternative medicines in the UK and the ongoing need for novel agents to treat acute and chronic disease led to the recognition that a revival of pharmacognosy was needed. Thus, it was through support from the dean, Alexander Florence, that there was reinvestment in the discipline and a new era in pharmacognosy at the Square began, 157 years after Anthony Todd Thomson's first lecture in 1842. Michael Heinrich, from the University of Freiburg, Germany, was appointed as head of the renamed Centre for Pharmacognosy and Phytotherapy in 1999. Today, with other new and existing appointments, the Centre has five academic staff (see Panel 2, p554). Sadly, not all aspects of pharmacognosy at the Square have thrived during the past five years. In 2002, land that included the school's medicinal plant garden at Myddleton House, Enfield, was sold and, today, staff at the centre work with plant material sourced from around the world.

Modern medicines from plants

The history of pharmacy was, for many centuries, identical with the history of its "first" subdiscipline — pharmacognosy. For hundreds of years, all *materia medica* was obtained from natural sources (mostly plants, but also minerals, animals and fungi).¹ Many of today's medicines are still derived from nat-



The Centre for Pharmacognosy and Phytotherapy is at the School of Pharmacy, Brunswick Square, London

ural sources and about one in four modern pharmaceutical drugs is of botanical origin. Natural sources (particularly plants) have yielded two different types of pharmaceutical product: pure chemical components, regulated as medicines; and phytopharmaceuticals or herbal medicines. Some of these are licensed as medicines whereas others are sold as unlicensed products. Scientific interest in herbal medicines is, to a considerable degree, driven by the public's use of, and interest in, these products. Individuals from almost all ethnic backgrounds rely on such medicines. There is, therefore, a need to investigate further the use of herbal medicines from a multidisciplinary perspective, including exploring the importance of these health care products in the UK, as well as their quality, safety and efficacy.

Herbal medicines in pharmacy

Community pharmacies are one of the main sources of herbal medicines. One aspect of Joanne Barnes's work is to explore pharmacists' experiences with herbal medicines and their users. Her research has shown that pharmacists are asked for, and provide advice and information on, herbal medicines and receive reports from users of suspected adverse drug reactions associated with their use. Pharmacists' involvement with herbal medi-

cines raises questions about their knowledge and practice, so further work has explored pharmacists' training in herbal medicines and their beliefs on the quality, safety and efficacy of these products.

Ongoing work is investigating trends in the teaching of pharmacognosy and related areas (herbal and complementary medicines) at UK schools of pharmacy and in methods of teaching pharmacy students about pharmacovigilance of herbal medicines. In another project, in collaboration with Linda Anderson (of the Medicines and Healthcare products Regulatory Agency) and David Phillipson, Dr Barnes provides information on herbal medicines for pharmacists, based on reviewing the scientific literature, through the publication 'Herbal Medicines'.² This text is supported by the Royal Pharmaceutical Society and continues the work begun in

The authors of this article are: **Joanne Barnes, PhD, MRPharmS, Paul Bremner, PhD, Simon Gibbons, PhD, FRSC, J David Phillipson, DSc, FRPharmS, and Michael Heinrich, Dr rer nat habil, MA.** They are all staff at the Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University of London. All, except Dr Bremner, are fellows of the Linnean Society

1986 by Carol Newall, Dr Anderson and Professor Phillipson. Dr Williamson also summarises information on medicinal plants and has published a new edition of 'Potter's herbal cyclopaedia'.³

Safety and pharmacovigilance

In recent years, there have been several high-profile safety concerns associated with herbal medicines which, together with the widespread use of these products, has raised awareness of the need to monitor safety and to develop pharmacovigilance practices.⁴ Within this, the perspectives and behaviours of users of herbal medicines should not be neglected because they can have important implications for the safe and effective use of these products.

Dr Barnes is investigating the use of herbal medicines, including concurrent use with prescription medicines, and users' behaviour towards reporting suspected adverse drug reactions. Her work also involves exploring the feasibility of monitoring the safety of herbal medicines purchased through community pharmacies and the potential role of the pharmacist. Dr Barnes's work on pharmacovigilance of herbal medicines extends to researching international issues and to investigating the practices of traditional Chinese herbal medicine (TCHM) retail outlets and practitioners with respect to the safe and effective use and supply of TCHMs.

Ethnopharmacy

The study of local and traditional knowledge is an area of scientific inquiry now commonly called ethnobiology. This relates specifically to medicinal plants as ethnopharmacology or ethnopharmacy. Professor Heinrich's research in this area focuses on the use of medicinal plants by indigenous groups in Mexico,⁵ Guatemala, Australia, Italy and Greece. One aim of this work is to preserve this rapidly changing knowledge for posterity and to find novel ways to ensure the transmission of this knowledge to future generations.

These projects seek to give new values to local traditions that have been used for many generations and are now at the brink of becoming forgotten. Similar questions arise with the diversity of medicinal plant usage by ethnic groups in the UK. Here, however, a goal is to identify how such knowledge and activities influence the use of NHS facilities and what beneficial or harmful effects the use of herbal remedies may have in these groups.

From user to molecular targets

Professor Heinrich's group, together with experts in molecular biology, has studied nuclear factor kappa B (NF- κ B) as a therapeutic target. NF- κ B is a transcription factor that was discovered almost 20 years ago. Its activation is pivotal in targeting numerous gene sites whose products are involved in innate immunity and anti-apoptotic activity. Thus, this protein (and the associated signalling cascade) is a target for drug discovery in many academic institutions and pharma-

ceutical companies, with the ultimate aim of discovering agents that will affect the NF- κ B cascade, with positive ameliorating effects in inflammation and cancer.

A recent project (AINP: anti-inflammatory natural products from plants), funded under the EU's fifth framework programme, resulted in multi-target evaluation of about 1,100 extracts from 255 ethnobotanically used plant species (mostly Mediterranean). The extracts were tested in a series of molecular assays relating to different aspects of NF- κ B activation. Compounds from these studies have been identified as NF- κ B inhibitors that play a role in apoptosis.⁶ Similarly, plants with antioxidant effects which, potentially, could provide leads for new nutraceuticals are currently under investigation in another EU-funded project.

Mechanisms, synergies and interactions

A new EU-funded collaborative project headed by Professor Heinrich and involving three industrial collaborators and six universities is investigating preparations derived from *Cannabis sativa* in the treatment of migraine

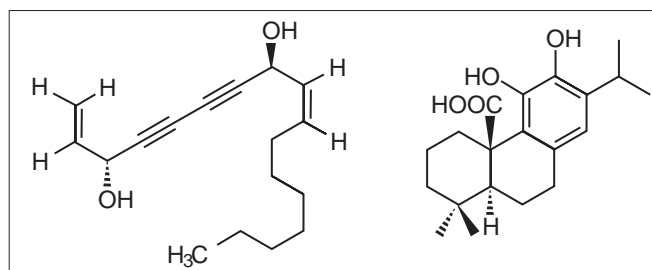


Figure 1: Falcarindiol (left) and carnosic acid

and arthritis. The work involves testing the effects of extracts using *in vitro* and *in vivo* pharmacological methods. Previous research by Dr Williamson has identified constituents of cannabis that could not only modify the action of other compounds present in the same plant but even have an opposite effect. Results comparing cannabis extracts with individual cannabinoids also supported one of the principles of herbal medicine, which suggests that a total herbal extract is more than just the sum of its parts, and confirms subjective experiences by patients.⁷ Cannabis has been an ongoing area of research at the school since the 1970s, when Jim Fairbairn undertook work exploring its cannabinoid content.

Dr Williamson's research also concerns the mechanisms of action of natural, including herbal, medicines. Using different examples

Panel 1: Pharmacognosy at the Square from 1842 to 1998

Senior staff

1842–1889

A. Todd Thomson, J. Pereira FRS
R. Bentley MRCS, J. R. Green FRS
E. M. Holmes*

1890–1998

H. G. Greenish†

T. E. Wallis*‡

J. W. Fairbairn DSc§

J. D. Phillipson DSc§

F. J. Evans DSc§

M. F. Roberts DSc‡

Research interests

Documentation, collection and characterisation of medicinal plants

Microscopical characterisation of medicinal plants

Quality assurance of medicinal plants by precise macroscopical and microscopical (including quantification) descriptions

Biological activities of laxative drugs and of cannabis; biosynthesis of natural drugs

Chromatographic separation and determination of chemical structures of active principles of medicinal plants; bioassay-guided fractionation to assist isolation of active principles of medicinal plants with antiprotozoal and central nervous system activities; herbal medicines

Irritant phorbol esters with pro-inflammatory and tumour promoting activities; biologically active principles of cannabis; herbal medicines

Enzyme control of alkaloid biosynthesis

* Curator of the museum of the Pharmaceutical Society. Part of the museum's pharmacognosy collection is now at the Royal Botanic Gardens, Kew.

† Dean of the School of Pharmacy

‡ Retired as reader in pharmacognosy

§ Retired as professor and head of department of pharmacognosy



The staff at the centre are investigating *Allium christophii* for compounds with antimicrobial activity

her research group has shown that there is a difference between the action of individual compounds from a medicinal plant and that of the whole extract.

It is also apparent that there is still much to be learnt about plant compounds whose actions were thought to be well-known, and that new mechanisms of action can still be discovered from “old” herbs. For example, a novel mode of action for thymol, from the herb thyme (usually better known as an antiseptic used in dentistry), at gamma-aminobutyric acid receptors was recently found.⁸

The potential for interactions between herbal and conventional prescription medicines has attracted much interest in recent years but there is a lack of basic and clinical research in this area. In a recently initiated collaboration with a UK producer of herbal medical products (Bioforce UK), Professor Heinrich, with Andreas Kortenkamp from the Square’s Centre for Toxicology, is investigating the effects of selected products on the cytochrome P450 system.

Pharmacopoeial standards

Dr Williamson is also involved with the British (as is Professor Phillipson) and European Pharmacopoeias, where chemical standards for herbal medicines are being determined to ensure consistency and reproducibility. These can be highly variable for natural products, but are essential for patient safety.

Antibacterial compounds from plants

No plant-derived antibacterials are used clinically. However, there are enormous challenges ahead in treating multidrug-resistant bacterial strains, so there is considerable incentive to discover new antimicrobial agents from plants.

Simon Gibbons’s group at the Square is conducting research into two main areas. The

first is the isolation and characterisation of antibacterial compounds from plants. This is targeted against strains of fast-growing mycobacteria and methicillin-resistant *Staphylococcus aureus* (MRSA), some of which are multidrug-resistant. Multidrug resistance is an increasingly prevalent mode of resistance in clinically relevant species, particularly in MRSA, which is exceptionally difficult to treat and eradicate. Strains of mycobacteria that cause tuberculosis and other life-threatening infections are also acquiring multidrug resistance and the group is screening plant extracts against some of these species.

Chromatographic separation of active antibacterial extracts leads to pure, plant-derived natural products which are then subjected to structure elucidation by high-field nuclear magnetic resonance spectroscopy and mass spectrometry. Antibacterials are then profiled against a panel of wild-type and resistant strains and compared against existing antibiotics to ascertain whether or not they are of sufficient potency to designate as antibiotic drug leads. An example from this work includes evaluation of *Angelica dahurica*. This plant grows wild in thickets in China, Japan, Korea; the roots are known as Bai Zhi in traditional Chinese medicine. Bioassay-guided fractionation of a hexane extract prepared from the roots led to the isolation of the polyacetylenic natural product faltarindiol (See Figure 1).

Active compounds

Activity of faltarindiol was tracked using MRSA and multidrug-resistant strains. The range of minimum inhibitory concentrations was 8–32 µg/ml, highlighting the potential of this natural product class as antibiotic-lead compounds.⁹

Another area of research is the characterisation of bacterial resistance modifying agents. A series of diterpene natural products

Panel 2: Staff at the Centre for Pharmacognosy and Phytotherapy

Joanne Barnes is a lecturer in phytopharmacy
Paul Bremner is a senior research fellow
Simon Gibbons is a senior lecturer in phytochemistry
Michael Heinrich is head of the centre
J. David Phillipson is emeritus professor
Elizabeth Williamson was a senior lecturer, and has recently moved to a new post at the University of Reading

from rosemary (*Rosmarinus officinalis*, Lamiaceae), a widely used culinary and medicinal member of the mint family, was recently characterised. One of these compounds, carnosic acid (See Figure 1), potentiated the activity of tetracycline and erythromycin against strains which pump out these antibiotics via multidrug-resistant mechanisms.¹⁰ Carnosic acid also inhibited the efflux of substrates for the NorA MDR efflux pump, the major characterised efflux mechanism in *S aureus*.

These examples of work at the centre show that pharmacognosy (and its numerous applications, from new drug discovery to phytotherapy) not only offers challenges and opportunities to pharmacists in practice, research and industry, but also benefits to patients with the development of plant- and other natural product-derived medicines.

References

1. Heinrich M, Barnes J, Gibbons S, Williamson EM. Fundamentals of pharmacognosy and phytotherapy. Edinburgh: Churchill Livingstone; 2004.
2. Barnes J, Anderson LA, Phillipson JD. Herbal medicines. A guide for healthcare professionals (2nd edition). London: Pharmaceutical Press; 2002.
3. Williamson EM. Potter’s herbal cyclopaedia. Saffron Walden: CW Daniel Co Ltd; 2003.
4. Barnes J. Pharmacovigilance of herbal medicines. A UK perspective. *Drug Safety* 2003;26:829–51.
5. Leonti M, Vibrans H, Sticher O, Heinrich M. Ethnopharmacology of the Popoloca, Mexico: an evaluation. *Journal of Pharmacy and Pharmacology* 2001;53:1653–69.
6. Bremner P, Tang S, Birkmayer H, Fiebich BL, Muñoz E, Marquez N, Rivera D, Heinrich M. Phenylpropanoid NF-κB inhibitors from *Bupleurum fruticosum*. *Planta Med* 2004;70:914–8.
7. Wilkinson JD, Whalley BJ, Baker D, Pryce G, Gibbons S, Constanti A, Williamson EM. Medicinal cannabis: is Δ9THC responsible for all its effects? *Journal of Pharmacy and Pharmacology* 2003;55:1687–94.
8. Priestley CM, Williamson EM, Wafford KA, Sattelle DB. Thymol, from thyme essential oil, is a positive allosteric modulator of human GABA-A receptors and a homo-oligomeric insect GABA receptor from *Drosophila melanogaster*. *British Journal of Pharmacology* 2003;140:1363–72.
9. Lechner D, Stavri M, Oluwatuyi M, Pereda-Miranda R., Gibbons S. The anti-staphylococcal activity of *Angelica dahurica* (Bai Zhi). *Phytochemistry* 2004;64:331–5.
10. Oluwatuyi M, Kaatz G, Gibbons S. Antibacterial and resistance modifying activity of *Rosmarinus officinalis*. *Phytochemistry* 2004;65:3249–54.