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Review

Phytochemistry and pharmacognosy

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Abstract

During the past 50 years there have been tremendous advances in chemical and biological techniques of analysis that have transformed research in pharmacognosy. The PSE has regularly held symposia of relevance to pharmacognosy and some of these are briefly reviewed in the area of natural products from higher plants. These symposia have charted the developments that link pharmacognosy with phytochemistry and illustrate the application of increasingly more sophisticated analytical techniques to the discovery of biologically active compounds. Plants have yielded clinical drugs, either as natural product molecules, or as synthetic modifications, particularly for chemotherapeutic treatment of cancer and malaria. Aspects of biotechnology, traditional medicines and herbal medicinal products are briefly discussed.

Keywords: Phytochemistry; Pharmacognosy; Natural products chemistry; Biological activities; Medicinal plants; Drug discovery

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1. Introduction

Science is not limited by human imagination, but experimental research is often limited by the currently available technology. As a pharmacognosy research student in 1957 when the Plant Phenolics Group was formed, the main chromatographic technique available was paper chromatography (PC), taking 48 h for development. The sole method of physical analysis for identification and structure determination of natural products was UV spectroscopy and each spectrum took hours of careful measurements. Melting points and mixed melting points were required with elemental analysis and molecular weight determination. Structure determination was obtained by degradative chemistry and identification of specific moieties of the molecule. The whole investigation was most time consuming.

Within a decade, there was a number of dramatic advances in analytical techniques including TLC and GC, IR, ^{1}H NMR and MS that were powerful tools for separation and structure determination. There was immense excitement for our group when, in 1961, our first TLC plate was sprayed after only a 30-minute solvent development, revealing 12 alkaloidal spots from a plant extract. Shortly afterwards our first 60 MHz NMR spectrum, crude by today's standards, showed the number of aromatic, olefinic, methoxyl and methyl protons present. Refinements and introduction of new analytical techniques greatly facilitated natural product research (Phillipson, 1995).

Pharmacognosy is not a familiar term, even to many scientists. Dictionary definitions generally define the subject as the study of crude drugs of plant and animal origin. The name is derived from the Greek words *pharmakon* (drug) and *gnosis* (knowledge). For many years pharmacognosy specialised in the authentication and quality, as assessed macroscopically and microscopically, of crude drugs that were mainly of plant origin. No scientific subject remains static and a modern definition of pharmacognosy is that it is the science of biogenic or naturally derived pharmaceuticals and poisons. It deals with medicinal plants as crude herbs or extracts, pure natural compounds and foods having health benefits (Heinrich et al., 2004). This modern definition, and explanatory rider, reflect the changes that have taken place in the past 50 years, particularly with the focus on phytochemistry and biological activities of natural products. The scope of pharmacognosy is also defined as the study of physical, chemical, biochemical and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources (American Society of pharmacognosy, 2005). Research in pharmacognosy includes phytochemistry, microbial chemistry, biosynthesis, biotransformations, chemotaxonomy and other biological and chemical sciences.

By the 1950s, plant drugs such as cinchona, digitalis, ipecacuanha and opium, had been replaced by their isolated active constituents. There were many medicinal plants that had not yielded active compounds, partly due to the analytical techniques of the day, and they had become clinically obsolete. The pharmaceutical industry was synthesising and marketing highly potent clinically effective drugs, e.g. amphetamines, barbiturates, sulphonamides and tranquillisers. The antibiotics and reserpine were among the few novel clinical drugs derived from natural sources and it was confidently anticipated that all drugs, including natural ones, would be produced synthetically. The outlook for pharmacognosy as an academic subject in the Pharmacy curriculum was bleak. There were, however, some signs of encouragement. France and Germany, in particular, continued to use medicinal herbs in medical practice and several strong academic university departments of pharmacognosy remained. The National Cancer Institute (NCI) in the USA had initiated a natural products anticancer screening programme and the Eli Lilly company had developed the alkaloids vinblastine and vincristine for cancer chemotherapy.

During the past 50 years, from the founding of the Plant Phenolics Group through to the PSE, there has been a continuation of regular scientific symposia that have covered a wide range of topics in the plant sciences, including pharmacognosy. The increasing sophistication of chemical techniques has been paralleled by a plethora of sensitive biological tests and these have been utilised to investigate plant species for their active constituents. Attendances at symposia have increased and the PSE has regularly held meetings with other scientific societies, e.g. the American Society of pharmacognosy (ASP) and the Society of Medicinal Plant Research (GA). Highlights of some meetings with pharmacognostical interest have been selected, on a personal basis, and are described in the following text. This account is not intended to be encyclopaedic but illustrative of the links between pharmacognosy and phytochemistry specifically in the area of natural products from higher plants.

2. PSE symposia and pharmacognosy

Pharmacognosy was involved with the Plant Phenolics Group during its early days and Jim Fairbairn of the Department of Pharmacognosy, The School of Pharmacy, University of London, edited the proceedings of the meeting on the Pharmacology of Plant Phenolics held in 1958 (Fairbairn, 1959). Twenty years passed before there was another symposium devoted to pharmacognosy.

2.1. Alkaloids

Alkaloids comprise one of the major groups of medicinally used plant constituents and Indole and Biogenetically Related Alkaloids was selected as the subject of a PSE meeting held in 1979 (Phillipson and Zenk, 1980). Several of these alkaloids were in clinical use, including reserpine (the first tranquilliser) and the dimeric indole alkaloids vinblastine and vincristine (anticancer agents). Other indole

alkaloids, not in clinical use, possessed potent pharmacological properties, e.g. strychnine (a muscle contractor) and the toxiferines (muscle relaxants). Broadening the scope of the meeting to biogenetically related alkaloids allowed quinine, quinidine and emetine to be discussed. The symposium brought together scientists with expertise in different subject areas including botany, isolation and separation methods, biosynthesis, synthesis (including biomimetic synthesis) and biological activities. Revisiting this text some 26 years later, it is evident that it is a time capsule representing the state of knowledge at that time. The theme of the symposium was plants as sources of potentially pharmacologically active molecules based on chemotaxonomy.

In 1979, it was known that indole-iridoid derived alkaloids were mainly found in species from the Apocynaceae, Loganiaceae and Rubiaceae. Many species from these families had not been investigated chemically and the analytical techniques of TLC, GC, HPLC, UV, MS and NMR were applied to the identification of alkaloids from herbarium specimens thus avoiding expensive expeditions for plant collecting (Bisset and Phillipson, 1971, 1976; Phillipson, 1982; Phillipson et al., 1978, 1982). The biosynthesis of many complex iridoid-derived alkaloids was of current interest and Meinhart Zenk and colleagues had established that condensation of tryptamine with secologanin led to the key intermediate 3α (*S*)-strictosidine, the precursor of different skeletal types of alkaloid including heteroyohimbines, strychnine and vinblastine (Phillipson and Zenk, 1980).

A similar symposium on the isoquinoline alkaloids was organised by the PSE in 1984 (Phillipson et al., 1985). Morphine and codeine from *Papaver somniferum* are important analgesics for the relief of serious and moderate pain. In 1984, many, but not all, species of *Papaver* had been investigated chemically whilst in the Annonaceae with some 2000 species, only 150 species had been investigated, yielding an array of isoquinolines. The biosynthesis of several isoquinoline alkaloids was under current investigation and Meinhart Zenk and colleagues discussed their results in identifying the step-by-step pathways and the associated enzymes involved. Dopamine yielded (*S*)-norlaudanosoline, the precursor of many 1-benzyltetrahydroisoquinoline and related alkaloids (Phillipson et al., 1985).

2.2. Biological activities of plant metabolites

During the 1980s, pharmacognosy research moved away from investigations of specific groups of natural products and began to concentrate on searching for novel compounds with biological activities. This trend is well exemplified by a PSE symposium held in 1986 (Hostettmann and Lea, 1987). In addition to the isolation, separation and structure determination of natural products, lectures described *in vitro* and *in vivo* biological testing procedures that could be used to identify biologically active compounds present in plant extracts. This was not a new concept and had previously been applied successfully by the NCI in its plant screening programme for new anticancer drugs. Several academics were involved in similar biological activity-led programmes of research, e.g. searching plants for anti-fertility agents (Farnsworth et al., 1975). A successful strategy for investigating plants for biologically active compounds proved to be initial screening followed by bioassay-guided fractionation to aid isolation of active constituents.

The 1986 PSE symposium covered a wide range of activities including acetylcholine antagonism, antihistamine, antibacterial, anticancer, antifungal, antihypertensive, antiprotozoal, antiviral, antispasmodic, immunostimulant and molluscicidal (Hostettmann and Lea, 1987). Protozoal infections are common causes of disease and death in tropical countries. Collaboration between pharmacognosists and protozoologists at the University of London established a research programme for investigating traditional medicines for activity against *Plasmodium falciparum*. This organism, which had developed resistance to chemotherapeutic drugs, is the causative protozoan in human tertiary malignant malaria and has killed millions of people worldwide. Similar research was described for molluscicidal compounds with potential use against schistosomiasis. By 1986, the NCI natural products programme had resulted in the discovery of a number of highly active anticancer compounds including taxol and camptothecin discovered by Monroe Wall and colleagues. A further theme of the 1986 meeting was the investigation of medicinal plants as immunostimulants. Hildebert Wagner and colleagues had isolated a range of active compounds from low molecular weight alkaloids and phenolics to polysaccharides. This meeting demonstrated beyond all reasonable doubt that there were many structurally diverse plant natural products with different biological activities that had great potential for new drug development (Hostettmann and Lea, 1987).

A joint meeting of the Phytochemical Societies of Europe and North America held at Miami Beach, Florida, in 1992 was devoted to the phytochemical potential of tropical plants (Downum et al., 1993). Because rain forests were diminishing, it had become a matter of urgency to investigate their plant species for biologically active constituents. One area of interest was the potential for isolating compounds with antimalarial properties from traditionally used plants. In the following years, the scope of these investigations expanded to include species of *Entamoeba*, *Giardia*, *Leishmania*, *Plasmodium*, *Toxoplasma* and *Trypanosoma* as test organisms. Active compounds isolated included anthraquinones, benzoquinones, bisbenzylisoquinolines, flavonoids, indoles, limonoids, naphthylisoquinolines and quassinoids (Phillipson, 1995, 1999a; Phillipson and Wright, 1991a,b; Wright and Phillipson, 1990). These investigations provided scientific evidence to support the use of medicinal plants used in traditional medicine for the treatment of protozoal diseases and provided templates for the development of potential novel drugs.

A further meeting of the PSE in 1994 continuing the theme of traditional medicines attracted delegates from

40 different countries (Hostettmann et al., 1995). Presentations covered ethnomedicine, biologically active natural products (e.g. antitumour, antimalarial, anti-inflammatory) and recent research on medicinal plants from African, Asian and S. American countries. Biological test procedures were becoming increasingly sophisticated as exemplified by the NCI natural products research programme: *in vivo* tests using models of murine leukaemia were replaced by *in vitro* screens using slower growing human tumour cell lines. The urgent need for antiviral agents for the treatment of AIDS had led NCI to use high throughput screening techniques using tens of 1000s of pure compounds and crude extracts. These programmes have produced a wide range of active compounds including alkaloids, chalcones, flavonoids, quassinoids and steroids. Lead compounds for anti-HIV activity emerged from this research and included prostratin (diterpene), michellamine (naphthylisoquinoline), calanolide A (prenylated coumarin) and conocurvane (trimeric quinone) (Hostettmann et al., 1995).

The ability to use automated high throughput screening for biological activities helped the pharmaceutical industry to renew its interest in plants as potential sources of novel drugs. An example of industrial-academic collaboration was briefly described at a joint meeting of the PSE and PSA at Halifax, Nova Scotia in 1994 (Phillipson, 1995). Ten Chinese medicinal plants with traditional reputations for CNS activities were selected for investigation. Extracts were tested in a series of radio-ligand receptor binding assays, including adrenoceptor (α1, α2, β), 5-HT (1,1A, 1C, 2), opiate, benzodiazepine, ion channels (Ca^{++}, K^{+}), dopamine (1, 2), adenosine 1, muscarinic, Na^{+}/K^{+} ATPase and GABA (A, B) receptors. All extracts (1 mg/ml^{-1}) were active in at least one assay. Bioactivity-guided fractionation resulted in the isolation of individual active compounds including indole alkaloids, proanthocyanins, flavonoids and triterpenes (Phillipson, 1995, 1999b).

Bioassay methods in natural product research and drug development was the theme of a 1997 PSE symposium (Bohlin and Bruhn, 1999). Screening methods for the detection and evaluation of biological activities of plant extracts were reviewed. High throughput screening for biological activities generates much data but fails to distinguish between known and novel compounds. Hence, a process of dereplication is required. The NCI dereplication strategy for its antitumour and HIV inhibitory screens utilised initial fractionation by HPLC with diode array detection. Fractions were plated into 96 microtitre well plates, daughter plates prepared enabling biological testing and MS-ES for molecular weight determinations.

Pharmaceutical industry collaboration with the University of Queensland resulted in the testing of more than 9000 plant and more than 2500 marine extracts. Biological activities were assessed by high throughput screening using receptors, enzymes and mechanism based cellular assays for cardiovascular, respiratory, gastrointestinal, autoimmune and analgesic activities. More than 200 biologically active compounds were identified within a 3 year period and the chemical structures of >50% were established within 24 h by utilising 600 MHz NMR techniques (Bohlin and Bruhn, 1999).

Industry pressure to bring innovative drugs to the market is greater than ever. Use of robotics and miniaturised screening formats allows >150,000 samples to be screened against targets in 2–3 weeks. In order to generate novel chemical entities with potential for new drug development, the technique of combinatorial synthesis has been developed. The sequencing of genes in the biosynthesis of the polyketide antibiotic erythromycin has resulted in the identification of some 28 domains. Repositioning the sequence of the genes enabled production of new ''unnatural'' natural products and offers a radical change in drug discovery (Bohlin and Bruhn, 1999).

The 1999 PSE symposium on bioactive carbohydrate polymers included information on polysaccharides with anti-inflammatory, anticancer and immunostimulant activities. Assay methods were described for determining the amounts of such polymers in body tissues and fluids as prerequisites for bioavailability studies. Structure determination of carbohydrate polymers requires sophisticated methods of analysis including enzymatic cleavage followed by high resolution NMR and MS (Paulsen, 2000). Recent developments in anti-inflammatory and anti-infective natural products were reviewed in a 2002 PSE symposium. Inhibitors of the pro-inflammatory transcription factor NF-κB, which is involved in the downstream signalling cascades of inflammatory conditions, provide leads to potential novel anti-inflammatory drugs. Parthenolide, aucubin and curcumin have been shown to be active inhibitors of NF-κB (Bremner and Heinrich, 2005). Combatting multi-drug resistant bacteria requires new classes of antibacterials and inhibitors of resistance mechanisms. Higher plants offer a possible source of such compounds and secondary products, including alkaloids, phenolics and terpenes, have been identified as active compounds (Gibbons, 2005).

2.3. Advances in techniques of phytochemical analysis

The separation, identification and structure determination of biologically active compounds has been facilitated by continual development of chromatographic and spectroscopic methods of analysis. PSE symposia have highlighted these developments, over the years, as they have been applied to phytochemistry. It was evident at the 1994 PSE symposium at Lausanne, Switzerland that these analytical techniques were becoming more and more sophisticated (Hostettmann et al., 1995). The NMR techniques of COSY and HETCOR were available for establishing connectivities between neighbouring protons and between linked ^{1}H and ^{13}C, INEPT being used for long range heteronuclear correlations over 2–3 bonds. The 1997 PSE symposium at Uppsala, Sweden,

featured the application of TLC, HPLC and HPLC coupled with UV photodiode array detection (LC-UV), LC-MS, electrospray (ES) and LC-NMR techniques for the separation and structure determination of antifungal and antibacterial plant compounds (Bohlin and Bruhn, 1999).

Currently available chromatographic and spectroscopic techniques in new drug discovery from natural products were briefly reviewed at the joint meeting of the PSE, ASP and GA symposium held in Amsterdam, 1999, to mark 2000 years of natural product research (Vlietinck, 2000). Computer modelling greatly assists spectrum interpretation and the generation of chemical structures meeting the spectral properties obtained. The computer systems utilise ^{1}H, ^{13}C, 2D-NMR, IR and MS spectral properties. Libraries of spectra can be searched for comparison with complete or partial chemical structures. Hyphenated chromatographic and spectroscopic techniques are powerful analytical tools that are combined with high throughput biological screening in order to avoid re-isolation of known compounds as well as for structure determination of novel compounds. Hyphenated chromatographic and spectroscopic techniques include LC–UV–MS, LC–UV–NMR, LC–UV–ES–MS and GC–MS.

2.4. Biotechnology

Biotechnological application of plant cell and tissue techniques has been an active area of research for many years (Barz et al., 1977) and a PSE symposium in 1988 concentrated on secondary plant products (Charlwood and Rhodes, 1990). Early aims of this research included the production of plant cultures that would provide high yields of medicinal drugs. The *Catharanthus* alkaloids vinblastine and vincristine were prime targets because they occur in low concentrations in the roots of the parent plant, are expensive to isolate and not easy to synthesise. The production of high-cost pharmaceuticals in good yields was not achieved, but some plant cultures did produce specific secondary products, e.g. anthraquinones, berberine, shikonin, in high amounts. Furthermore, some plant cultures yielded novel compounds including alkaloids, phenylpropanes, quinones and terpenes (Rutyer and Stockigt, 1989).

Plant cell culture production of secondary metabolites became a competitive area of research involving different scientific disciplines, including pharmacognosy. Cultures producing low yields of alkaloids were developed in our department from medicinal plants such as *Cinchona ledgeriana*, *Datura candida* and *P. somniferum* (Phillipson, 1995). Attempts to produce the antimalarial artemisinin from cultures of *Artemisia annua* were unsuccessful but a series of flavonoids was isolated. Some of these flavonoids exerted weak activity *in vitro* against *P. falciparum* but, surprisingly, were shown to have a potentiating effect on the activity of artemisinin (Elford et al., 1987). Antiplasmodial quassinoids were not isolated from cultures of *Ailanthus* or *Brucea*, but high yields of canthin-6-one alkaloids (1.27–2.0%) were obtained. Biosynthetic studies of selected secondary metabolites from medicinal plant species were undertaken and attempts made to manipulate cultures to produce high yields of biologically active metabolites (Phillipson, 1995).

Among the most exciting scientific achievements of plant cell culture research has been the successful elucidation of the step-by-step biosynthetic pathways, at the enzyme control level, of many indole, isoquinoline and tropane alkaloids (Zenk, 1991, 1995). The gene encoding for strictosidine synthetase has been cloned and expressed in *E. coli* so that the transformed cultures fed with tryptamine and secologanin produced strictosidine, the key intermediate of many of the biologically active indole alkaloids. Leads to new drug discovery and biotechnology have been reviewed (Verpoorte, 2000). Proteins can be produced by modification of plant cultures (e.g. vaccines) and micro-organisms (e.g. insulin).

3. Phytochemistry and the development of novel clinical drugs

3.1. Naturally occurring plant molecules

Over half of the world's top 25 best-selling pharmaceutical drugs in 1991 owed their origin to natural products (Kinghorn and Balandrin, 1993). These drugs include the ACE inhibitors enalapril and captopril, the non-steroidal anti-inflammatory agents diclofenac and naproxen, the antibiotics amoxicillin/clavulanic acid, the β2-agonist salbutamol and the immunosuppressant ciclosporin. Higher plant-derived products represent around 25% of the total number of clinically used drugs and include the classical drugs atropine, codeine, digoxin, morphine and quinine.

During the past 50 years, plants have provided several more clinically used drugs. The *Catharanthus* alkaloids vinblastine and vincristine, currently used for the treatment of leukaemias, lymphomas and some solid tumours, were introduced through the Eli Lilly Company in the 1960s. The NCI collaborative research programme into natural products with anticancer activity was initiated by Jonathan Hartwell in 1957. Between 1960 and 1986 more than 35,000 species and 108,330 extracts were screened against murine tumours and from 11 compounds approved for extensive tumour panel testing, 2 came into clinical use.

An extract of the bark of the Pacific yew, *Taxus baccata*, was shown to be highly active in the KB anti-tumour test in 1964 by Monroe Wall and colleagues (Kingston, 2000). It was not until 1971 that the chemical structure of the active compound taxol (paclitaxel) was determined. Interest in taxol was renewed in 1979 when it was shown that it promoted the assembly of tubulin into stable microtubules

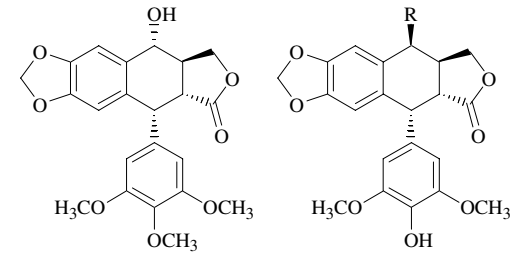
and, eventually, in late 1980, it was introduced into clinical practice. Currently, taxol is used for the treatment of ovarian cancer and in the secondary treatment of breast cancer. Camptothecin was isolated from the fruits of *Camptotheca acuminata* by Monroe Wall and colleagues in 1966. It was subsequently shown to be a topoisomerase I inhibitor and in 1993 was still undergoing clinical investigation (Kinghorn and Balandrin, 1993).

Artemisinin was isolated as the active principle of the Chinese traditional antimalarial herb *A. annua* by Chinese scientists in 1972. Artemisinin is a sesquiterpene containing a highly unusual endoperoxide moiety and is currently in clinical use for the treatment of cerebral malaria. Galantamine (galanthamine) is an alkaloid obtained from snowdrops, *Galanthus nivalis*, and other species of Amaryllidaceae. It has recently been introduced clinically for the treatment of mild to moderate Alzheimer's disease. Galantamine is a reversible inhibitor of acetylcholinesterase and slows down the progression of the disease, but does not cure it (Heinrich et al., 2004).

3.2. Improving on nature

Natural product drugs have provided many challenges for synthetic chemists. There are several reasons why a naturally occurring drug may be synthesised, e.g. some plant species have become threatened due to over collection from the wild, or the costs of collection, extraction and isolation may have proved too high for marketing. Also, synthetic analogues may be prepared in attempts to improve water solubility, pharmacological or safety profiles. For many years, natural molecules have acted as templates for the synthesis of new drugs and there are numerous examples of synthetic drugs that are based on the structure of a natural product molecule, e.g. the analgesic pethidine was based on morphine and the antimalarial mefloquine on quinine.

New synthetic and semisynthetic analogues of natural products have continued to be developed during the past 50 years. Although *Podophyllum* species have reputations for treating cancers, podophyllotoxin **1**, and related lignans, were shown in the 1950s to be too toxic for clinical use. Some 40 years later, attempts were made to modify their toxicity and poor water solubility resulting in the introduction of new clinical agents. Etoposide **2** is used for the treatment of small cell lung cancer, lymphomas and testicular cancer, whereas teniposide **3** is used to treat brain tumours. Both of these semisynthetic drugs are epimeric at position 1 to podophyllotoxin and differ markedly in their mode of action. Podophyllotoxin binds to tubulin and the modified drugs are topoisomerase II inhibitors, preventing DNA synthesis. Semisynthetic analogues of vinblastine **4** and vincristine **5** in clinical use include vindesine **6** (treatment of leukaemia and lung cancer) and vinorelbine **7** (breast cancer) (Kinghorn and Balandrin, 1993).



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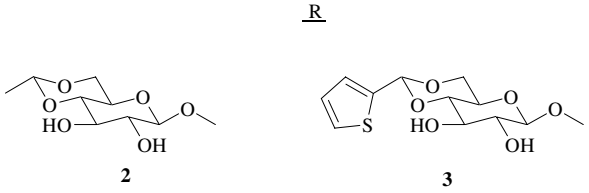
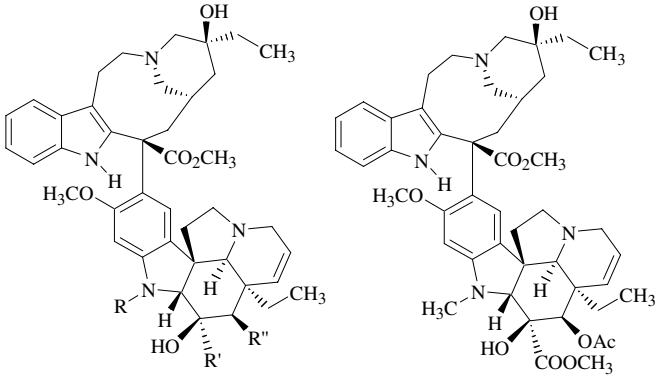


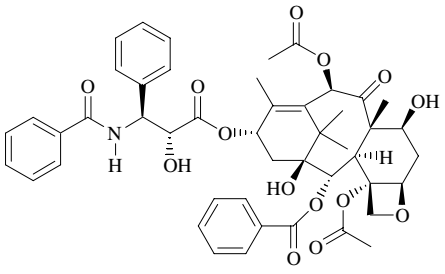
2 **3**



	R	R'	R''
4	CH_3	CO_2CH_3	OAc
5	CHO	CO_2CH_3	OAc
6	CH_3	$CONH_2$	OH

7

Taxol **8** is obtained as a minor component from the bark of mature trees of *Taxus brevifolia* and if sourced as such for anticancer chemotherapy, would result in massive loss of the species. Partial synthesis is used for commercial production utilising 10-deacetylbaccatin III **9** which occurs in high yields in the needles (a renewable source) of *Taxus* species. A semisynthetic analogue, taxotere **10**, is used in adjuvant treatment of breast cancer and non-small cell lung cancer (Kingston, 2000). Camptothecin **11** co-occurs with other alkaloids including 10-hydroxycamptothecin **12** which proved to be more active in anticancer test systems. Further modifications to the molecule were made to improve water solubility and lower toxicity resulting in two new clinical drugs, topotecan **13** and irinotecan **14**. Topotecan (9-dimethylaminomethyl-10-hydroxy-20(*S*)-camptothecin) is used in the treatment of metastatic ovarian cancer and irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin) is used to treat colorectal cancer (Kinghorn and Balandrin, 1993).



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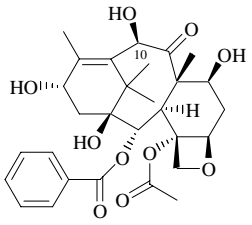

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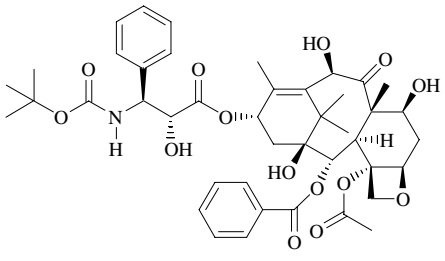

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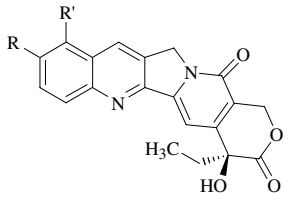
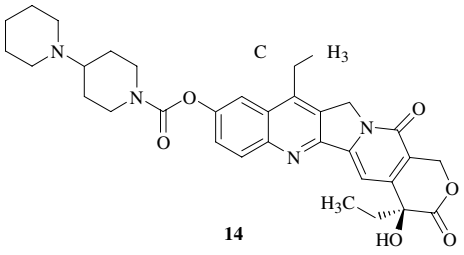
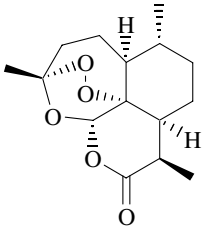


	R	R'
11	H	H
12	OH	H
13	OH	$CH_2N(CH_3)_2$



14

The antimalarial drug artemisinin **15** is hydrophobic and some semisynthetic derivatives are in clinical use. Reduction of the lactone carbonyl yields dihydroartemisinin and derivatisation of the secondary alcohol functions into ethers (e.g. artemether **16**, arteether **17**) or esters (e.g.sodium artesunate **18**, a hemisuccinate water soluble derivative) has resulted in alternative antimalarial drugs (Phillipson, 1995). Artemether is used clinically in the UK in combination with other antimalarial drugs. Synthetic tricyclic 1,2,4-trioxanes **19** based on the endoperoxide moiety of artemisinin have proved to be potently active *in vivo* against *Plasmodium berghei* (Phillipson, 1995). A readily synthesised trioxolone **20** has been selected for clinical development as an antimalarial drug (Vennerstrom et al., 2004). The bulky adamantine ring protects the sensitive endoperoxide bridge and the amide side chain confers water solubility.



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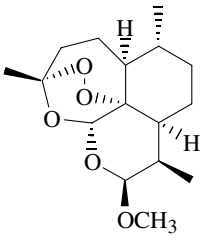

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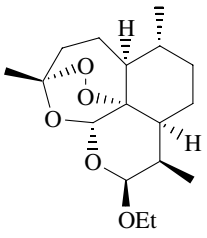

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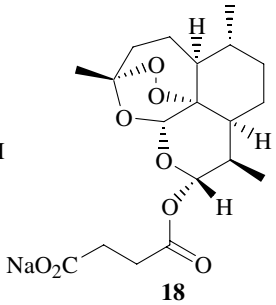

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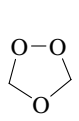

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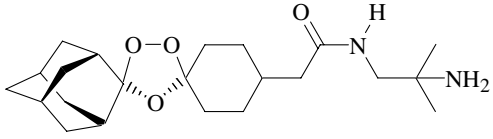

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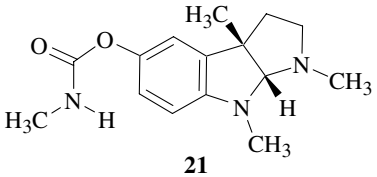

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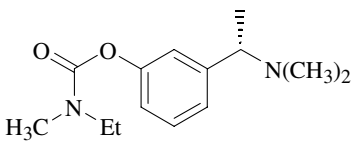
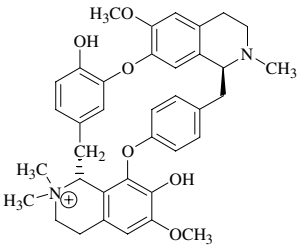


22

Physostigmine **21** is the template model for rivastigmine **22** used in the treatment of Parkinson's disease. It has similar pharmacological action and clinical uses as galantamine. Tubocurarine **23**, is a bisbenzyltetrahydroisoquinoline neuro-muscular blocking agent of tube curare obtained from *Chondrodendron tomentosum*. This alkaloid has served as a template molecule for the development of a series of clinically used drugs, e.g. decamethonium, suxamethonium and pancuronium, used as muscle relaxants in surgical operations reducing the need for deep anaesthesia. Such drugs tend to remain active after surgical procedures have been completed. In the early 1980s, collaboration between John Stenlake and colleagues at Strathclyde University, Glasgow and the Wellcome Company resulted in the clinical introduction of atracurium **24**. This new drug had a half life of 20 min and was degraded enzymatically in the body by ester hydrolysis and also non-enzymatically by Hofmann elimination (Waigh, 1988). Atracurium is a mixture of 10 isomers and the single isomer cisatracurium is more potent and provides cardiovascular stability.



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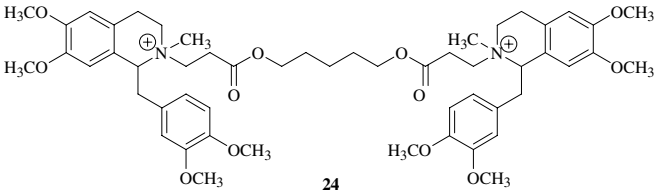

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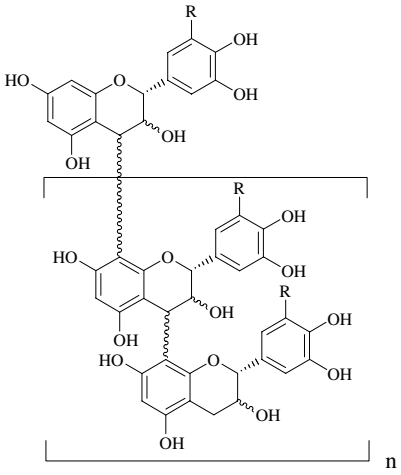


25 R = H or CH_3

n = 1, 2, 3, 4, etc

4. Traditional medicine and ethnopharmacology

The roles of ethnobotany in drug development and of ethnopharmacology in drug discovery, particularly in Mexico, have been reviewed (Heinrich, 2000; Heinrich and Gibbons, 2001). Many people in developing countries continue to rely on traditional medicine practitioners and local medicinal plants for their primary health care (WHO, 1995). In 1997, it was estimated that about 20% of the world's population lived in extreme poverty and lacked basic medicines (WHO, 1997).

The pharmaceutical industry tends to concentrate on diseases that mainly affect populations of affluent countries, e.g. cancer, cardiovascular diseases, because it has to recoup the massive costs involved in bringing new medicines to the market. The expanding chemical and biological analytical techniques that have become available for natural products research has enabled academic departments of pharmacognosy to investigate traditional medicines (e.g. Bohlin and Bruhn, 1999; Downum et al., 1993; Hostettmann and Lea, 1987; Hostettmann et al., 1995). This research has focussed on providing scientific evidence for the presence of active principles in traditional medicines, for their standardisation and for assessments of toxicities. The identification of new biologically active compounds also provides leads for new drug development.

The investigations of plants with traditional reputations for the treatment of malaria and other protozoal diseases that have been undertaken in pharmacognosy at the School of Pharmacy, University of London, have been briefly described previously (Section 2.2). The following two examples illustrate the role that pharmacognosy can play in the investigation of traditional medicines.

4.1. Dragon's blood

The blood red sap, known as Dragon's Blood, of the bark of some *Croton* species is used in S. America for the treatment of wounds, cancer and rheumatism. These species are threatened with extinction because of the popularity of Dragon's Blood for medicinal purposes. The sap of *Croton lechleri* bark obtained from Ecuador contained more than 90% proanthocyanidins **25**, mainly monomers to heptamers of flavan-3-ol units (Cai et al., 1991). Five novel dimers and trimers were isolated and characterised in addition to the known compounds (+)-catechin, (−)-epicatechin, (+)-gallocatechin, (−)-epigallocatechin and dimeric procyanidins B1 and B4. A series of minor constituents was also isolated, including four novel clerodane diterpenes crolechinol **26**, crolechinic acid **27**, and korberins A **28** and B **29** (Cai et al., 1993a,b). Biological testing of individual compounds demonstrated antibacterial and anti-inflammatory activities and proliferation of endothelial cell growth (Chen et al., 1994).

4.2. Traditional Chinese medicine prescription and eczema

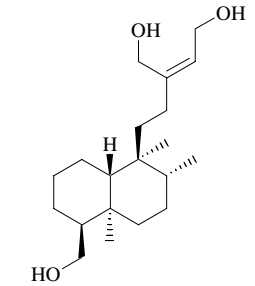
Clinicians at Great Ormond Street Hospital for Sick Children in London noted marked improvements in some

of their young patients suffering from severe atopic eczema. These improvements proved to be due to the use of a TCM oral remedy supplied by a Chinese herbal practitioner and not to the hospital treatment. Aqueous extracts of a mixture of 10 Chinese herbs and a placebo were given to 37 children under clinical trial conditions and shown to be clinically effective in the treatment of their eczema. Four individual herbs were selected for initial chemical and biological investigations in the search for a postulated active ingredient. Extracts of each of the four herbs showed marked anti-inflammatory activity in a mouse *in vivo* test but when the four were combined and given to a few child eczema patients there was no clinical effect. The number of herbs was increased to seven on the basis of one having sedative activity in mice and two being used in TCM for the treatment of urticaria and, again, no clinical improvements were observed. Clinical efficacy depended on the presence of all 10 herbs present in the TCM prescription (Phillipson et al., 1994; Phillipson, 1995).

5. Herbal medicines in Europe

Despite all of the advances made by the pharmaceutical industry in the development of novel and highly effective medicines for the treatment of a wide range of diseases, there has been a marked increase in the use of herbal medicines in the more affluent countries of the world. Germany has the largest share of the market in Europe and it was reported that the sales of herbal medicinal products (HMPs) in 1997 were US$ 1.8 billion (Barnes et al., 2007). Numerous scientific medical/pharmaceutical books have been published in recent years aiming to provide the general public and healthcare professionals with evidence of the benefits and risks of herbal medicines (Barnes et al., 2007; ESCOP, 2003; Tyler, 1993; Wichtl, 1994). Industry has met the increased demand for herbal medicines by manufacturing a range of HMPs many of which contain standardised amounts of specific natural products. Because of the public use of herbal medicines there has been a need for up-to-date monographs, e.g. the European Pharmacopoeia now contains 125 monographs on specific medicinal herbs and a further 84 are currently in preparation. In preparing such monographs, it is essential to have a knowledge of phytochemistry for defining the chemical profiles of medicinal herbs and an understanding of analytical tests for identification of the herbs and for the quantitative assessment of any known active ingredients.

Advances in chemical and biological analytical techniques (see Sections 2.2 and 2.3) have facilitated investigations into many of the popular herbal medicines that are used in Europe, e.g. HMPs containing *Echinacea* species and *Ginkgo biloba*. HMPs containing *Echinacea* species are widely used in the belief that they stimulate the immune system and help to prevent infections such as colds and influenza. Three species of *Echinacea* are used in HMPs and they contain complex mixtures of constituents including alkamides, caffeic acid derivatives, polyacetylenes and polysaccharides (Bauer, 1999; Barnes et al., 2007). Biological activities *in vitro* and *in vivo* include stimulation of phagocytosis and cytokines (IL1, IL6, IFN α/β), antiviral, formation of prostaglandins and leukotrienes. *Ginkgo biloba* HMPs are used to treat cognitive deficiency. Products are standardised on their ginkgolide (A, B and C, **30**, **31**, **32**, respectively,diterpenes) and flavonoid (e.g. gingetin, **33**) contents. Despite numerous clinical trials, there are no licensed medicinal products of Echinacea and Ginkgo in the UK.



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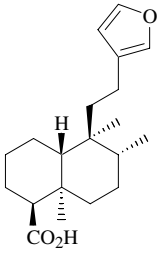

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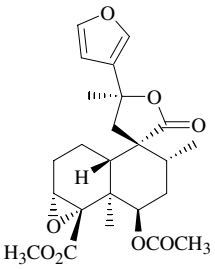

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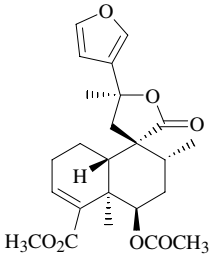

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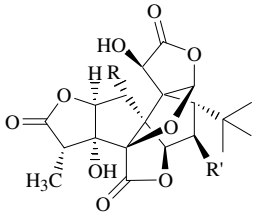
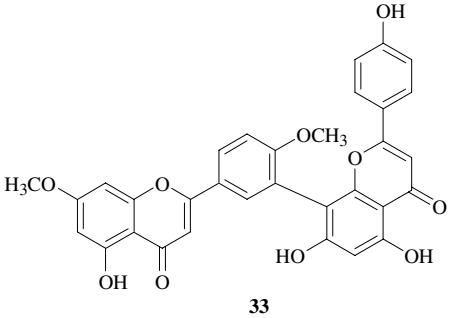


30 R = H, R' =H
31 R = OH, R' = H
32 R = OH, R' = OH



33

Even though there are sophisticated methods of analysis available, there are still considerable gaps in our knowledge

of the active principles of many of our herbal medicinal plants. Valerian root, for example, is used for the relief of sleep disturbances related to mild anxiety and is present in a number of popular HMPs. The known constituents include iridoids (valepotriates such as valtrate, dihydrovaltrate, isovaltrate) and volatile oil (complex mixture of terpenes), but the active principles of valerian remain unidentified.

5.1. Safety and efficacy of herbal medicines

The majority of herbal medicines used in Europe is safe when used at recommended dosages, but it is recognised that some may cause adverse effects, including drug interactions in patients concurrently taking other medicines. St John's wort, *Hypericum perforatum*, used for the treatment of mild to moderate depression, interacts with digoxin, HIV inhibitors, theophylline and warfarin. Some medicinal herbs, when ingested, either affect cytochrome P450 isoenzymes by which drugs are metabolised, or, phosphoglycoprotein transporter systems that affect drug distribution and excretion. Concurrent use of some herbal medicines with other medicines may either lower blood plasma concentrations of medicinal drugs, possibly resulting in suboptimal therapeutic amounts, or lead to toxic concentrations in the blood.

There are many medicinal herbs and HMPs, particularly from China and the Indian subcontinent, that are imported into the UK with constituents that are not declared on their labels. Some Chinese HMPs have been shown to contain medicinal drugs such as antibiotics, anti-inflammatory agents and corticosteroids, while some Indian HMPs include toxic metals, e.g. lead and mercury.

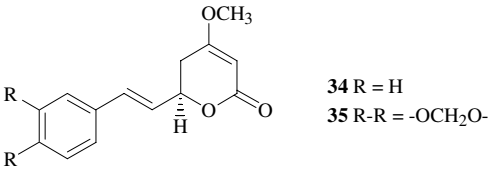
There have also been several high profile cases of adverse effects following ingestion of herbal medicines containing toxic constituents, e.g., *Aristolochia* species and kava (*Piper methysticum*). A slimming preparation manufactured in Belgium included *Aristolochia fangchi*, a known toxic plant. This only became apparent when several women developed severe kidney damage. The toxic constituents are substituted nitrophenanthrene carboxylic acids, which are nephrotoxic, carcinogenic and mutagenic, causing kidney failure and cancer (De Smet, 1992). To date, more than 100 cases of renal failure are known and at least 18 women have developed cancer. *Aristolochia* species and products are banned in the UK. Kava, the root of *Piper methysticum*, is obtained from Polynesia in the S. Pacific, where it has many uses including relaxing the mind, easing pains and inducing sleep. HMPs containing kava were manufactured in the USA and claims made for their ability to ease anxiety. These HMPs became popular but subsequently were associated with hepatotoxicity and they were banned in several countries, including the UK, in 2003. The UK ban was recently re-evaluated, but there was no evidence to justify reversing the decision (MHRA, 2006a). There are currently 110 cases of hepatotoxicity recorded from 9 countries including 9 fatalities and 11 patients requiring kidney transplants. The major constituents of kava are lipophilic kavalactones including kavain **34**, methysticin **35**, dihydrokavain **36**, dihydromethysticin **37**, yangonin **38** and dihydroyangonin **39**. The toxic constituents are not the kavalactones and it will require collaboration between phytochemists and toxicologists to establish the toxic principles.

Herbal medicines are, of course, used for their reputed beneficial effects, and there is now an increasing body of clinical evidence from randomised controlled clinical trials to support the efficacy of certain herbal medicines for specific indications. However, many early clinical trials assessing herbal medicines did not meet contemporary standards for evaluating medicines, and/or involved poorly defined herbal medicinal products. It is essential that all HMPs undergoing clinical trials (and indeed preclinical experiments) should be chemically standardised to provide optimum and consistent pharmaceutical quality, thus enabling other researchers to replicate existing work and allow comparisons between results obtained from studies assessing products produced by different manufacturers.

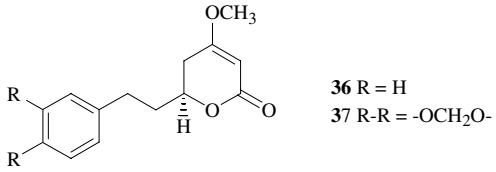
In 2004, the European Union introduced new legislation to control HMPs, The Directive on Traditional Herbal Medicinal Products (Directive 2004/24/EC). This Directive requires that all HMPs that are not licensed as medicines will have to be registered as Traditional Medicines in the member states. HMPs not registered by 30 April 2011 will have to be withdrawn from the market. Registered HMPs will have to meet requirements on quality, safety and efficacy. Quality assessment is paramount and all products will have to be manufactured in accordance with the principles of Good Manufacturing Practice and manufacturing premises will be subject to inspections. The manufacturers will have to provide bibliographic evidence of safety and efficacy in the treatment of minor ailments without having to undertake clinical and toxicological evaluations that are mandatory for licensed medicinal products. Registered HMPs will have had to be in use for 30 years, although evidence of 15 years' use in other countries may be included.

In 2005, the Medicines and Healthcare products Regulatory Agency (MHRA) established a new Herbal Medicines Advisory Committee (HMAC) in the UK to provide independent advice on quality, safety and efficacy of Traditional Herbal Medicines to the Minister of Health. The HMAC is currently dealing with safety issues associated with some HMPs, e.g. Black Cohosh, *Cimicifuga racemosa* (MHRA, 2006b). The ability to comment on these issues requires a knowledge of phytochemistry and pharmacognosy. Black Cohosh is present in a number of HMPs widely available in the UK for the treatment of menopausal symptoms. By 31 May 2006 there were 31 reports of suspected adverse reactions to black cohosh, including jaundice, dark urine, nausea, tiredness and abdominal pain. The MHRA has advised members of the public to stop taking these products and to seek medical advice if such symptoms occur (MHRA, 2006b). The high demand for black cohosh has threatened its existence in the wild and lower cost Chi-

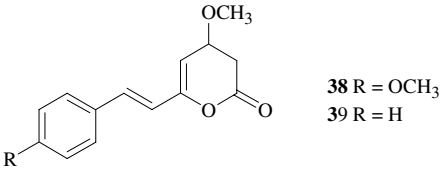
nese species of *Cimicifuga* have been used as substitutes in some HMPs. Correct botanical identification of raw herbal material is essential in order to distinguish between *Cimicifuga racemosa* and other species. A fingerprinting analytical technique has been reported and is based on HPLC photodiode array/MS/evaporative light scattering (HPLC/PDA/MS/ELSD) that distinguishes *C. racemosa* from other species (He et al., 2006). The triterpene glycoside cimigenol-3-*O*-arabinoside **40** and the furochromones cimifugin **41** and its 3-*O*-glucoside **42** have been shown to be specific markers for *C. racemosa* and distinguish it from 2 other N. American and 7 Asiatic species (Jiang et al., 2006). Analysis of 11 commercially available black cohosh products for triterpene glycosides and phenolic constituents by HPLC/PDA and selective ion monitoring LC/MS has shown significant product-to-product variability. Some products labelled as including *C. racemosa* did not contain this species.



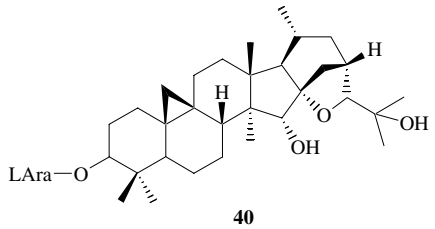
34 R = H
35 R-R = -OCH_2O-



36 R = H
37 R-R = -OCH_2O-



38 R = OCH_3
39 R = H



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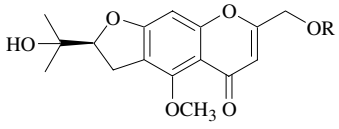

41 R = H
42 R = glu

6. Conclusions

There have been tremendous developments in chemical and biological techniques of analysis since the PSE and its forerunner societies were established 50 years ago. In the intervening years, the PSE has regularly organised symposia highlighting the progress of medicinal plant research that have been of particular relevance to pharmacognosy and phytochemistry. Plant natural products with anticancer and antimalarial activities have been two major research areas (Cragg and Newman, 2005; Newman and Cragg, 2007; Wright, 2005). The millennium provided a time for reflection on medicinal plant research (Kinghorn, 2001,2002; Verpoorte, 2000; Vlietinck, 2000) and the 50th anniversary of the GA was another opportunity to review progress in medicinal plant research (Phillipson, 2003).

It is evident that medicinal plant research is interdisciplinary and that international collaboration exists between different scientific disciplines including botany, biochemistry, pharmacognosy, pharmacology, phytochemistry, medicine, toxicology and biotechnology. Pharmacognosy, based for many years in botanical methodology, embraced phytochemistry and the new sensitive methods of analysis for identifying, characterising and determining chemical structures of natural products. The parallel developments of sensitive methods for assessing biological activities enabled research to focus on the active constituents of plants.

The past 50 years has seen the introduction of novel natural product drugs into clinical use, e.g. vinblastine, vincristine, taxol, artemisinin, galantamine, and also semisynthetic analogues of natural products, e.g. vindesine, vinorelbine, taxotere, etoposide, teniposide, irinotecan, topotecan, artemether, sodium artesunate and atracurium. In the 1950s, the pharmaceutical industry had little interest in plants as sources of novel drugs and it was confidently anticipated that the majority of novel drugs, and the existing natural drugs, would be produced by chemical synthesis. The introduction of vinblastine and vincristine into cancer chemotherapy coupled with the NCI natural product anticancer screening programme, awakened the possibility that plants could be useful in drug discovery and development. The advent of high throughput screening methods for assessment of large numbers of plant extracts containing putative biologically active compounds further encouraged industrial interest in plant research.

The unravelling of biosynthetic pathways has allowed greater understanding of the ways in which plants synthesise natural products and have enabled genetic technology to produce natural and related "unnatural" related compounds. There is now a parallel development to combinatorial synthesis, namely combinatorial biosynthesis (Bohlin and Bruhn, 1999). Will such technologies lead to future novel clinical drugs? Whatever new techniques come on stream, it is evident that there will be a continued need for novel drugs in the treatment of disease. Drug resistant tumours, multi-drug resistant pathogenic organisms, Parkinson's and Alzheimer's diseases, and chronic anti-inflammatory diseases are among the areas for much

needed new drugs, particularly with novel modes of action.

In the 1950s, it would not have been possible to predict that in 50 years time there would be a thriving industry producing HMPs based on the public demand for herbal medicines. Certainly it would not have been envisaged that in 2006 there would be a need for expertise in pharmacognosy and that, in the UK, pharmacognosists would be appointed to national committees such as the HMAC dealing with advice on herbal medicines. The recently retired dean of the School of Pharmacy, University of London, in his valedictory address to the council of the Royal Pharmaceutical Society of Great Britain acknowledged that "*in Pharmacy we have made errors in predicting the future, eradicating subjects like pharmacognosy*" (Florence, 2006).

Will the new technologies available today preclude the continuing investigation of plants as sources of novel drugs? Only time will tell. However, it is encouraging to realise that there is support for research into plant medicines. An editorial published in the *Lancet* indicated that Western Medicine would do well to embrace the herbal pharmacopoeias from countries such as China with its long history of herbal medicines, and cited as an example the development of the antimalarial drug artemisinin (Anon, 2006). Pharmacognosy is an exciting subject for research and I remain optimistic that medicinal plants will continue to contribute to healthcare as well as producing novel clinically useful drugs.

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