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Review Article

Pharmacognosy in the 21st century*

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Abstract

The term pharmacognosy as a constituent scientific discipline of pharmacy has been in use for nearly 200 years, and it refers to studies on natural product drugs. During the last half of the 20th century, pharmacognosy evolved from being a descriptive botanical subject to one having a more chemical and biological focus. At the beginning of the 21st century, pharmacognosy teaching in academic pharmacy institutions has been given new relevance, as a result of the explosive growth in the use of herbal remedies (phytomedicines) in modern pharmacy practice, particularly in western Europe and North America. In turn, pharmacognosy research areas are continuing to expand, and now include aspects of cell and molecular biology in relation to natural products, ethnobotany and phytotherapy, in addition to the more traditional analytical method development and phytochemistry. Examples are provided in this review of promising bioactive compounds obtained in two multidisciplinary natural product drug discovery projects, aimed at the elucidation of new plant-derived cancer chemotherapeutic agents and novel cancer chemopreventives, respectively. The systematic study of herbal remedies offers pharmacognosy groups an attractive new area of research, ranging from investigating the biologically active principles of phytomedicines and their mode of action and potential drug interactions, to quality control, and involvement in clinical trials.

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Introduction

The term pharmacognosy was first used between 1811 and 1815, and originally referred to ''materia medica'', the knowledge of drug materials or pharmacology. It is derived from two Greek words, *pharmakon* (a drug) and *gignosko* (to acquire a knowledge of) (Evans 1996). Later on, pharmacognosy became restricted to that branch of pharmacy investigating ''medicinal substances from the plant, animal and mineral kingdoms in their natural, crude, or unprepared state, or in the form of such primary derivatives as oils, waxes, gums, and resins'' (Hocking 1997). Although this latter definition may have been appropriate for the descriptive and microscopical applications of pharmacognosy which were developed from the 19th century until the middle of the 20th century (Pratt & Youngken 1956; Wallis 1967), it became necessary for the subject to be redefined as it subsequently broadened in scope to deal with the chemical components of crude drugs. For example, pharmacognosy was stated to be ''an applied science that deals with the biologic, biochemical, and economic features of natural drugs and their constituents'' (Tyler

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et al 1988). In a further attempt to update the scope of this field in a manner consistent with scientific activities ongoing at the beginning of the 21st century, pharmacognosy has recently been defined as "a molecular science that explores naturally occurring structure–activity relationships with a drug potential" (Bruhn & Bohlin 1997).

The transition of pharmacognosy from a descriptive botanical discipline to one having more of a chemical focus was spearheaded in the US in the 1960s and 1970s by Arthur E. Schwarting, while he was at the University of Connecticut (Tyler & Tyler 1992). Other early pharmacognosist pioneers of this trend in the US have included Egil Ramstad of Purdue University (Agurell & Ramstad 1962), Varro E. (Tip) Tyler of the University of Washington and Purdue University (Benedict et al 1962), Jack L. Beal, of Ohio State University (Doskotch et al 1969), and Norman R. Farnsworth of the University of Pittsburgh and the University of Illinois at Chicago (Farnsworth et al 1966), to name but a few. Some of the early pharmacognosists in the UK with a chemical focus in their work were James W. Fairbairn (Fairbairn 1964) and Edward J. Shellard (Phillipson & Shellard 1967), both of the University of London, and Francis Fish, of the University of Strathclyde (Calderwood & Fish 1966). There have been a great many other distinguished chemically-oriented pharmacognosists who have made equivalent scientific contributions in the last 40 or 50 years to those mentioned above, particularly in continental Europe and East Asia. Prominent among this illustrious group are René R. Paris of the University of Paris V in France (Paris & Delaveau 1962), Egon Stahl, from the University of Saarbrücken in Germany (Stahl 1971), Ludwig Hörhammer and his successor, Hildebert Wagner, of the University of Munich (Wagner & Hörhammer 1971), Otto Sticher of the Swiss Federal Institute of Technology, Zurich, Switzerland (Sticher 1969), and Japanese academics such as Shoji Shibata, of the University of Tokyo (Nagai et al 1966), and Tsunematsu Takemoto, of Tohoku University and later Tokushima Bunri University (Takemoto et al 1966). All of those mentioned above, some of whom are still active in the field, built up academic groups that provided training to many younger pharmacognosists and natural product scientists. Examples of the work of some of these younger colleagues are included in the References of this review. Without the impetus such distinguished scientists provided, pharmacognosy as a discipline and speciality branch of academic pharmacy would not be anywhere near so well developed as it is at the onset of this new millennium.

Today, at the beginning of the 21st century, pharmacognosy teaching and research is pursued enthusiastically by its disciples in academic departments of pharmacy all over the world. Although the name pharmacognosy may be substituted in certain countries by terms such as phytochemistry or pharmaceutical biology, the areas of research embraced by natural products may include aspects of analytical chemistry, bioactive compound discovery, bioassay method development, biocatalysis, biosynthesis, biotechnology, cell biology, chemotaxonomy, clinical studies, cultivation of medicinal plants, ethnobotany, genetics, marine chemistry, microbial biotransformation, molecular biology, organic synthesis, pharmacology, phytochemistry, phytotherapy, the standardization of traditional medicines, taxonomy, tissue culture, and zoopharmacognosy (the study of self-medication of medicinal plants by primates and other animals) (Ageta et al 1998; Luijendijk et al 1999). As elaborated on in an earlier review, research in pharmacognosy and natural products has undergone a great renewal of interest in recent years (Verpoorte 2000). Several specialist peer-reviewed international scientific journals on various aspects of pharmacognosy and natural products research have their main editorial offices in departments of pharmacy or pharmacognosy or else are edited by a trained pharmacognosist, including *Biochemical Systematics & Ecology*, the *Journal of Ethnopharmacology*, the *Journal of Natural Products* (formerly *Lloydia*), *Natural Medicines* (formerly *Shoyakugaku Zasshi*), *Pharmaceutical Biology* (formerly the *International Journal of Pharmacognosy*), *Phytomedicine*, *Phytotherapy Research*, *Planta Medica* (the *Journal of Medicinal Plant Research*), and the book series *The Alkaloids: Chemistry and Biology* (Academic Press, San Diego). Mention should also be made of a second extensive book series, *Medicinal and Aromatic Plants: Industrial Profiles* (Harwood Academic Publishers, Reading), to which many pharmacognosists have edited volumes or contributed chapters. Worldwide, pharmacognosy-based scientific societies are flourishing, including the American Society of Pharmacognosy, Association Française pour l'Enseignement et la Recherche en Pharmacognosie (France), Gesellschaft für Arzneipflanzenforschung (Europe), the Korean Society of Pharmacognosy, and the Japanese Society of Pharmacognosy. These societies typically organize an annual meeting for members, award travel and research grants, and promote the publication of scientific journals and newsletters. The American Society of Pharmacognosy is most likely typical in welcoming into its membership ranks many talented natural products scientists who did not train in pharmacy as an undergraduate degree.

For about 50 years, the proportion of the undergraduate or professional pharmacy curriculum devoted to pharmacognosy has been in decline in certain countries, as noted by others (Farnsworth 1979; Shellard 1981; Houghton 1997). Moreover, fewer departments or schools of pharmacy have retained pharmacognosy as a discrete subject in the curriculum as other basic pharmaceutical and biomedical science and clinical aspects have become more prominent, particularly in the UK and the US. However, the situation is not all gloom and doom for the subject, since a recent analysis of faculty positions in pharmacognosy shows strong representations in pharmacy departments in countries such as France, Germany, Japan and Turkey (Barnes 2000). At this point in time, pharmacognosy is perhaps most strongly represented in Japan, where natural products has long been one of the strongest areas of chemistry, in large part because of the traditional use of natural remedies there (Ageta et al 1998; Nakanishi 1999). However, even in the UK and the US, the recent substantial increase in the use of herbal remedies in pharmacy practice has rekindled interest in pharmacognosy and natural products in general among pharmacists and pharmacy students alike (Houghton 1994; Croom & Walker 1995; Tyler 1999a). This increased interest in herbal products by the pharmaceutical profession has been paralleled by an increased awareness in this topic and other forms of alternative medicine by physicians (Goldbeck-Wood et al 1996; O'Hara et al 1998).

The chemical aspects of pharmacognosy have benefited enormously from the widespread availability of powerful spectroscopic techniques, particularly mass spectrometry and nuclear magnetic resonance, coupled with effective chromatographic methods for the purification of organic molecules from crude solvent extracts (Cordell 1995; Phillipson 1995). Some of the early phytochemical work in pharmacy departments tended to focus on looking for new sources of prescription drugs, for example, chemotaxonomic studies on bisindole alkaloids from the genus *Catharanthus* (Farnsworth et al 1966) and indole alkaloids from *Rauwolfia* alkaloids (Court et al 1967). It was quickly realized in the more research-oriented pharmacy academic institutions, however, that it was necessary to incorporate an element of biological testing with phytochemical work (Farnsworth 1979; Evans & Taylor 1983; Hamburger & Hostettmann 1991). Incorporation of a bioassay into the process of chromatographic purification has permitted the purification of one or more bioactive substances from the crude extracts prepared from organisms by bioactivity-guided fractionation (Ghisalberti 1993). Of particular mention here is the logistically simple brine shrimp lethality ''bench top'' bioassay developed by the pharmacognosist Professor Jerry L. McLaughlin and co-workers at Purdue University (Meyer et al 1982), which has been shown to be appropriate to direct the screening of cytotoxic and anti-tumour compounds from plants (Anderson et al 1991). This inexpensive in-vivo technique has become widely used in natural products chemistry and even synthetic organic chemistry laboratories around the world. Many primary and secondary bioassays appropriate for the screening of natural product crude extracts, purified chromatographic fractions, and pure isolates have been developed, and can be varied accordingly depending on whether the desired outcome of the research is a pharmaceutically or agrochemically relevant target compound (Hostettmann 1991; Ghisalberti 1993; Williamson et al 1996; Bohlin & Bruhn 1999; Houghton 2000).

In this review, two major facets of current research being conducted by pharmacognosy groups will be covered, namely, natural product drug discovery and the scientific investigation of herbal remedies (phytomedicines). Given the broad range of such activities that are taking place around the world, it is not possible to cover all of these in this review. However, the reader can be referred to recent literature for descriptions of aspects of biosynthesis (Ageta et al 1998), biotechnology (Verpoorte 2000), marine chemistry (Koenig & Wright 1996), pharmaceutical botany (Ageta et al 1998), and phytochemistry (Ageta et al 1998), compiled or being performed by pharmacognosy and pharmaceutical biology groups.

Drug Discovery from Natural Products

The importance of drugs from animal, microbial, and higher plants is well established, with such natural products also serving as lead compounds for semi-synthetic manipulation and as templates for total synthetic modification (Balandrin et al 1985; Sneader 1985; Kinghorn & Balandrin 1993; Bruneton 1995; Evans 1996; De Smet 1997; Shu 1998; Cragg et al 1999; Samuelsson 1999; Simmons & Grayer 1999). It has been estimated that up to 50% of the prescriptions presently dispensed in the US may contain one or more natural product drugs, with this term broadly defined so as to include various types of molecular modification (Robbers et al 1996). While there was a trend in the middle of the 20th century to remove many old botanical drugs from official compendia, as many new synthetic and microbially-derived drugs appeared (Shellard 1981), several new small-molecule natural product-derived

drugs have been introduced into therapy in western countries in recent years, including acarbose, artemether, capsaicin, docetaxel, dronabinol (the synthetic form of Δ^9-tetrahydrocannabinol), galanthamine, irinotecan, paclitaxel, tacrolimus (FK-506), and topotecan (De Smet 1997; Shu 1998). This trend is likely to continue in the future, at least for the treatment of certain disease states, such as cancer and infectious diseases, based on the high proportion of compounds entering clinical trials that are either natural products per se, or semi-synthetic compounds based on natural product template molecules (Cragg et al 1997).

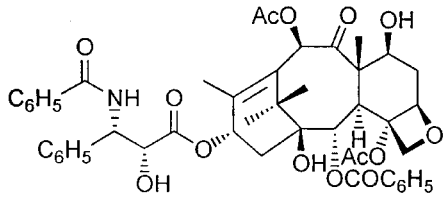
Accordingly, there remains considerable interest in the screening of organisms in drug discovery programmes, since structurally-novel chemotypes with potent and selective biological activity may be obtained, and considerable biodiversity exists (Gullo 1994; Clark 1996; Harvey & Waterman 1998; Young 1999; Newman et al 2000). These organisms may be fungi, marine fauna and flora, microorganisms such as actinomycetes and bacteria, and plants (Gullo 1994). In a recent statistical survey, it was pointed out that when compared with libraries of synthetic substances, natural products offer the prospects of discovering a greater number of compounds with sterically more complex structures (Henkel et al 1999). The same authors determined that the origin of 30000 bioactive natural products could be divided between animals (13%), bacteria (33%), fungi (26%) and plants (27%) (Henkel et al 1999). The potential diversity of bacteria and fungi is particularly large, with some 5000 out of $>$ 40000 bacteria, and only 70000 out of as many as 1.5 million fungi, having even been identified, let alone investigated in the laboratory (Young 1999). In the next few paragraphs, higher plants will be considered specifically, since this group of organisms has been studied the most by pharmacognosy groups around the world.

Only a relatively small percentage (5–15%) of the approximately 250000 higher plants has been systematically investigated for the presence of bioactive compounds (Kinghorn & Balandrin 1993; Cragg et al 1997). As many as 155000 seed plants occur in the tropics, with some 120000 in the tropical moist forests alone, attesting to their great biotic richness (Soejarto & Farnsworth 1989). Tropical rain forest plants occupy only 7–8% of the land surface on earth, but offer a disproportionate opportunity for the discovery of stucturally-novel, biologically-active substances (Kinghorn & Balandrin 1993). This has been attributed to the high humidity, elevated temperature, and species density, along with a continuous growing season, which have led tropical rain forest plants to produce specialized secondary metabolites as pollination attractants and as defensive substances against predators and parasites (Artuso 1997). However, there is a pressing need for the conservation of the biodiversity of the tropical rain forests as a consequence of the alarming degree of erosion due to increasing encroachment by human populations (Soejarto & Farnsworth 1989; Artuso 1997).

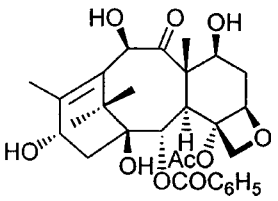
Plants offer the scientist searching for novel bioactive compounds the added advantage of ethnobotanical observations, since many species are used in systems of traditional medicine, mainly in developing countries (Balick 1990; Mata et al 1991; Sticher 1995; De Smet 1997; Heinrich et al 1998). It has been estimated that nearly 75% of about 120 biologically active plant-derived substances used in the world were discovered by following up on leads from traditional medicine (Soejarto & Farnsworth 1989). However, great concern has been expressed about the prospects of indigenous knowledge of ethnomedicine lasting far into this new millennium (Cox 2000). The ethnobotanist Mark Plotkin has reflected on the problem of the imminent loss of shamans in the world's tropical rain forests very adroitly, as follows: ''In a conservation context, we stand at the end of a precipice. We are scrambling to find ways to save the rain forest, yet thousands of years of accumulated human wisdom—the knowledge to use the forest, without destroying it, to benefit humankind—is going to vanish over that precipice within the next generation. Throughout the tropics the species are disappearing, but the knowledge to use those species is disappearing at an even faster rate. Each time one of these medicine men (or women) dies, it is as if a whole library has gone up in smoke'' (Plotkin 1993).

Depending on the selection of the in-vitro and in-vivo bioassays used to monitor the crude extracts, chromatographic fractions, and pure isolates of a plant or other organism, natural products research can be focussed on a particular type of disease. Thus, the following paragraphs will summarize some of the progress made recently on the discovery of potential plant-derived anticancer agents and naturally occurring cancer chemopreventives in two separate multidisciplinary collaborative research projects at the University of Illinois at Chicago. Other groups in pharmacy academic institutions have described natural product research directed toward other disease targets, such as anti-fungal agents (Clark & Walker 2000), anti-mycobacterial agents (Newton et al 2000), anti-malarial agents (Phillipson 1999), anti-viral agents (Vlietinck et al 1997), and hypoglycemic agents (Lamda et al 2000).

In the US, each day approximately 1500 people die of cancer, with about double this number diagnosed with



1 Paclitaxel (Taxol)

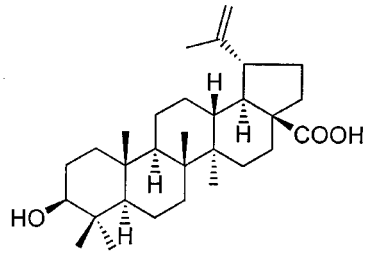


2 10-Deacetylbaccatin III

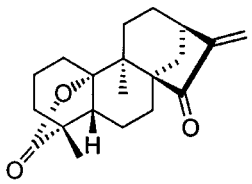
Figure 1 Structures of paclitaxel (Taxol) and 10-deacetylbaccatin III.

invasive cancer. On a world-wide basis, the incidence of cancer is superseding the increase in the population (Kinghorn et al 1999). Among the many advances in cancer therapy, cancer chemotherapeutic agents based on plant secondary metabolites have played a part, and there are now 11 such compounds based on four structural classes (bisindole alkaloids, camptothecin derivatives, epipodophyllotoxins, and the taxanes) used clinically in the US (Wall & Wani 1996; Dutcher et al 2000; Kingston 2000). The taxane diterpenoid, paclitaxel (Taxol; Figure 1, **1**), is worthy of special mention, since this was the first chemically-unmodified plant constituent for over 25 years to have been approved by the Food and Drug Administration (FDA) in the US, when it came onto the market as an anti-cancer agent in the early 1990s (Suffness 1995). This compound, isolated initially with the trivial name taxol from the bark of the Pacific yew (*Taxus brevifolia* Nutt.; Taxaceae), is now produced semi-synthetically from 10-deacetylbaccatin III (Figure 1; **2**) extracted from ornamental yew species, and has become the biggest selling anticancer agent ever in the US, with sales of over $1 billion per year (Kingston 2000). Paclitaxel was listed as eighteenth in the 1999 list of top-selling medicines, and is now being used to treat an expanding range of cancer types. Needless to say, the clinical and commercial success of paclitaxel has played an extremely important role in stimulating further exploratory research to discover additional novel compounds from plants. In addition, several additional potential plant-derived anti-cancer agents are presently undergoing preclinical or clinical trials (Cragg et al 1997; Shu, 1998). Accordingly, there is an enduring interest in investigating the plant kingdom further, with the aim of discovering additional new classes of compounds with anti-cancer activity (Cassady & Douros 1980; Potier 1992; Cragg et al 1999; Kinghorn et al 1999; Lee 1999; Itokawa et al 2000).

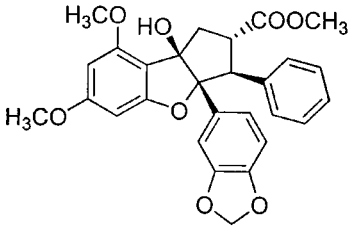
In an effort to discover novel anti-cancer agents of plant origin, our team at the University of Illinois at Chicago (UIC) is performing collaborative work with groups from a private research institute (Research Triangle Institute (RTI), Research Triangle Park, North Carolina) and a major pharmaceutical company (Bristol-Myers Squibb, Princeton, New Jersey). This project is funded by the US National Cancer Institute, under their National Cooperative Natural Products Drug Discovery Groups programme. This project is now in its third five-year phase, with Glaxo Wellcome Medicine Research Centre, Stevenage, UK having been the industrial partner with UIC and RTI during the period 1990–1995. Each year, 400–500 primary plant samples are collected, mainly from tropical regions, but also from the southern US. The species are identified by collaborating botanists in each host country, and priority is afforded to species that are endemic in the particular country concerned. Although as a policy decision, plants are not collected in this programme on an ethnomedical basis, for about 70% of the species collected there is no previous phytochemical or biological testing information available in the literature (Kinghorn et al 1999). Plants are collected only after formal signed agreements with host countries are in hand, with changes in the legal expectations, due primarily to international treaties (particularly the United Nations Convention on Biological Diversity convened in Rio de Janeiro in 1992), national legislation, and professional self-regulation, having made it much more difficult to collect samples for so-called biodiversity prospecting than was formerly the case (Gollin 1999). Our group has developed a standard extraction scheme suitable for the screening of dried plant samples, in which the chloroform-soluble extracts are subjected to a detannification step by washing with sodium chloride solution to remove vegetable tannins, which tend to interfere with protein-based bioassays (Wall et al 1996). The organic-solvent crude extract of each plant acquisition is screened in a panel of about 25 cell-based and enzyme-inhibitory and receptor-binding mechanism-based in-vitro bioassays housed at the three primary sites in the consortial group, including high-throughput screening procedures at our partner pharmaceutical company. Before performing activity-guided fraction-



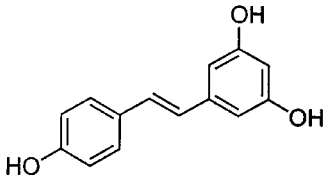
3 Betulinic acid



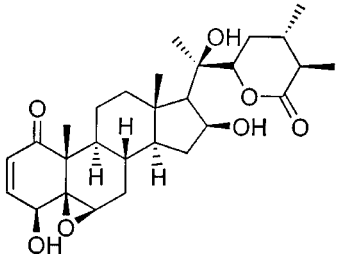
4 15-Oxozoapatlin



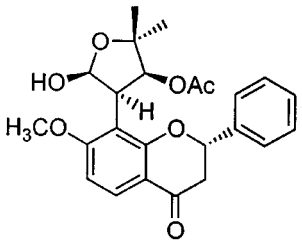
5 4′-Demethoxy-3′,4′-methylenedioxy-methyl rocaglate



6 *trans*-Resveratrol



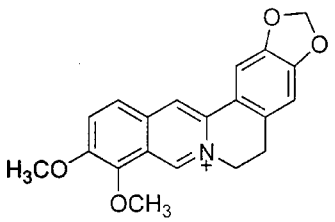
7 Withaphysacarpin



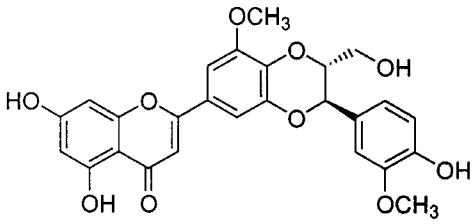
8 Tephrorin A

Figure 2 Structures of promising bioactive natural products obtained from two drug discovery projects.

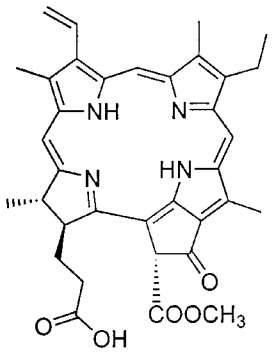
ation of a promising lead, a dereplication step is taken, in an attempt to detect active compounds of previously known structure present in the crude extract. This involves subjecting the active extract in a standard HPLC system, passage through a UV detector at 280 nm, and splitting the stream into two. The smaller portion is treated and then passes into a mass spectrometer, while the larger portion is fractionated into a 96-well plate, with each well then evaluated in the bioassay in which the initial activity was found. In this manner, it is possible to obtain the masses of the active compounds in the wells and then to compare these data with information in the NAPRALERT and other databases (Constant & Beecher 1995; Kinghorn et al 1999). Several hundred biologically active compounds have been obtained in this collaborative project thus far,



9 Berberine



10 5′-Methoxyhydnocarpin D



11 Pheophorbide *a*

Figure 3 Structures of compounds showing synergistic antibacterial activity.

representative of a wide range of plant secondary metabolites. Examples of active compounds which have come from this programme to date are betulinic acid (Figure 2; **3**) from *Ziziphus mauritiana* Lam. (Rhamnaceae), 15-oxozoapatlin (Figure 2; **4**) from *Parinari curatellifolia* Benth. (Chrysobalanaceae), and the novel compound 4′-demethoxy-3′,4′-methylenedioxy-methyl rocaglate (Figure 2; **5**), from *Aglaia elliptica* Bl. (Meliaceae). Betulinic acid was shown to be selectively active for a human melanoma cancer cell line, and to exhibit in-vivo activity in a mouse xenograft model bearing human melanoma (Pisha et al 1995). Both 15-oxozoapatlin (Lee et al 1996) and 4′-demethoxy-3′,4′-methylenedioxy-methyl rocaglate (Cui et al 1997) have been selected for in-vivo xenograft testing at the National Cancer Institute, following successful evaluation in a number of preliminary tests.

An alternative approach to combating cancer by intervention with natural products involves their use as potential cancer chemopreventive agents. Cancer chemoprevention has been defined as "a prevention or delay process of carcinogenesis in humans by the ingestion of dietary or pharmaceutical agents" (Sporn et al 1976). There has been a considerable amount of work on the cancer chemopreventive effects of extracts and purified constituents of culinary herbs, fruits, spices, teas, and vegetables, which have been shown to inhibit the development of carcinogenesis in long-term animal models (Ho et al 1994; Huang et al 1994). However, at this point, there are no natural product-derived cancer chemopreventive drugs on the market, although a number of plant secondary metabolites are of interest for future clinical trials, including curcumin, ellagic acid, and phenethyl isothiocyanate (Kelloff et al 1994).

In our collaborative project on cancer chemopreventive agents, which has been ongoing since 1991, novel compounds are also isolated from crude plant extracts by activity-guided fractionation, with a different panel of bioassays used than in the project described above on anti-cancer agents. The project is again funded by the US National Cancer Institute, with all of the laboratory work carried out at the University of Illinois at Chicago, and there being several different scientific components (plant acquisition, phytochemistry, in-vitro and in-vivo biology, synthetic chemistry, and technical core support) (Kinghorn et al 1998; Pezzuto et al 1999). A primary focus of the overall project is on the collection of edible plants from around the world. Preliminary

biological evaluation of an organic-soluble extract from each acquisition occurs in about ten in-vitro assays germane to each of the initiation, promotion, and progression stages of carcinogenesis (Pezzuto et al 1999). Biological follow-up testing is conducted using a mouse mammary organ culture assay (Mehta et al 1994), and, in a very few selected cases, in-vivo evaluation in a two-stage mouse skin and/or a rat mammary carcinogenesis model (Udeani et al 1997). As in the previously mentioned project, more than one hundred compounds have been isolated with activity in one or more bioassays, representative of a wide array of secondary metabolite structural types. Examples include resveratrol (Figure 2; **6**) from *Cassia quinquangulata* Rich. (Leguminosae), withaphysacarpin (Figure 2; **7**) from *Physalis philadelphica* Lam. (Solanaceae), and the new flavonoid, tephrorin A (Figure 2; **8**), from *Tephrosia purpurea* Pers. (Leguminosae), which is a flavanone containing an unusual tetrahydrofuran moiety. Resveratrol, which also occurs in grapes and red wine, was found to be active as an inhibitor of cyclooxygenase 1, and then to show significant activity in the mouse mammary organ culture assay and in a full-term mouse skin carcinogenesis study (Jang et al 1997). Both withaphysacarpin (Kennelly et al 1997) and tephrorin A (Chang et al 2000) are inducers of the phase II drug metabolizing enzyme NAD(P)H : quinone reductase as evaluated in cultured Hepa 1c1c7 cells. Withaphysacarpin is of particular interest, since the fruits of its plant of origin (commonly known as the tomatillo) are used in the Latin American diet to produce green salsa, and in-vivo biological testing of this compound is currently taking place.

From the examples provided above from these two natural product projects related to cancer, it can be seen that interesting new biological observations may be made in a multidisciplinary setting for even very common compounds such as betulinic acid and resveratrol. Moreover, by strict adherence to activity-guided fractionation techniques, it is still possible to obtain new active compounds of considerable structural interest, even from comparatively well-investigated species such as *Tephrosia purpurea*. It can be expected that future natural product drug discovery projects will involve the need to go literally to the ends of the earth, to obtain previously unstudied organisms which may be logistically quite hard to obtain. In addition to the intended discovery of new drugs, such programmes can afford useful information concerning the protein and other cellular targets of small-molecule natural products. It is worth pointing out that natural product drug discovery projects, similar to the two described above, will increasingly require that participating pharmacognosists collaborate with scientists in other disciplines, such as analytical chemists, biochemists, biostatisticians, medicinal chemists, molecular biologists, organic chemists, pharmacologists, structural biologists, taxonomists, and toxicologists. Moreover, it is necessary for academic institutions to make a considerable investment in infrastructure in support of such research work. In addition to the need for properly equipped phytochemical and biological testing laboratories, it is also necessary to have access to facilities to process plants or other organisms (maintaining an inventory, taxonomic authentication, milling, small- and large-scale extraction, and storage), as well as having the appropriate means of cultivating selected species. A large amount of information is generated on the collection details of organisms, and on the biological data of extracts, chromatographic fractions and pure compounds, so it is necessary to process this information electronically. Central administrative support from the institution is also needed, as for example, the involvement of legal and international offices to help formulate agreements with authorities in the source countries of plants or other organisms of interest.

Studies on Herbal Medicines

In many developing countries of the world, there is still a major reliance on crude preparations of plants used in traditional medicines for their primary health care (Soejarto & Farnsworth 1989). In countries such as India and the People's Republic of China, the systems of traditional medicine are particularly well developed, and both of these have provided interesting new drug leads for potential development in western medicine. Moreover, a number of clinical evaluations of herbal medicinal preparations have already been conducted in certain western countries (De Smet 1997). As alluded to earlier, a major change has occurred in the interest of health professionals in western countries concerning the use of herbal remedies over the last decade, which in large part mirrors the increasing interest held by the public in terms of self-medication with botanical products. For pharmacognosists employed in institutions of pharmacy education, this new awareness of natural products has come as a major "shot in the arm", and a number of useful texts on the analysis, uses and/or potential toxicities of herbal remedies have appeared recently, which not only assist with teaching in pharmacy professional or undergraduate curricula but also serve as useful guides in pharmacy practice (e.g. Bisset 1994; Newall et al 1996; Wagner & Bladt 1996; Robbers & Tyler 1999; Cupp 2000).

Not only has the "herbal remedy revolution" created new opportunities for the teaching of pharmacognosy, but also this phenomenon has served to stimulate research in a new field of direct relevance to human health care. There may be some who might well demur at what they see as the unchallenging prospect of working on phytomedicines, since much is already known about many of these. However, the eminent organic chemist, Professor Koji Nakanishi, of Columbia University in New York, has thrown down the gauntlet in terms of the types of research hurdles that will need to be overcome in future work on herbal remedies and related medicinal plants, as follows: "That natural medicines are attracting renewed attention is encouraging from both practical and scientific viewpoints; their efficacy has been proven over the centuries. However, to understand the mode of action of folk herbs and related products from nature is even more complex than mechanistic clarification of a single bioactive factor. This is because unfractionated or partly fractionated extracts are used, often containing mixtures of materials, and in many cases synergism is most likely playing an important role. Clarification of the active constituents and their modes of action will be difficult. This is nevertheless a worthwhile subject for serious investigators." (Nakanishi 1999).

Many phytochemical and biological groups have already begun to perform laboratory work in a meaningful way on herbal remedies. For example, recent papers have appeared for common herbal remedies in terms of the development of analytical methodology (Hoberg et al 2000); isolation procedures for reference compounds (Millar 1998); the characterization of new chemical constituents (Shao et al 2000); the identification (Butterweck et al 2000), structure elucidation (Foo et al 2000), biosynthesis (Fiehe et al 2000) and chemical reactivity (Valcic et al 2000) of bioactive principles of phytomedicines; active compound mechanism of action determination (Bork et al 1999); and the toxicological evaluation of phytomedicine components (Kennelly et al 1999). A potentially far-reaching observation in terms of the safety of consuming certain herbal teas was made recently, when it was realized that two hepatotoxic otosenine-type pyrrolizidine alkaloid macroester constituents of the Chinese traditional medicine, *Ligularia hodgsonii* Hook. (Compositae), which is used as an antitussive, are soluble in both organic solvents and water. Although pyrrolizidine alkaloids based on otosenine are not particularly common, whenever they do occur in herbal teas they will thus be water-soluble when in the hydrophilic ionized form, and hence potentially toxic (Lin et al 2000).

The concept of several active principles acting in a synergistic manner in herbal remedies may be somewhat unusual to pharmaceutical scientists who are more used to activity in a medicinal preparation being due to a single therapeutic agent (Nakanishi 1999; Phillipson 1999). However, a recent example may be given of this phenomenon, with reference to constituents of the plant *Berberis freemontii* Torrey (Berberidaceae), a plant once used in Native American traditional medicine. It has been found that the anti-bacterial activity of berberine (Figure 3, **9**) from *B. freemontii* against a resistant strain of *Staphylococcus aureus* was potentiated by the addition of two further constituents of the plant, the flavonolignan, 5′-methoxyhydrocarpin D (Figure 3; **10**), and the porphyrin, pheophorbide *a* (Figure 3; **11**). Although either compound **10** or **11** potentiated the effects of a subthreshold concentration of the alkaloid, neither possessed antibiotic activity when tested alone (Stermitz et al 2000a,b). Berberine is also present in high concentration levels in the widely used herbal remedy Goldenseal (the rhizomes of *Hydrastis canadensis* L.; Ranunculaceae) (Bruneton 1995; Robbers et al 1996), so it is possible that synergistic biological effects occur between this protoberberine alkaloid and other known or as-yet unidentified constituents of this phytomedicine.

In a recent review article, Tyler (1999b) has outlined some of the scientific challenges that ensuring the safe and effective use of herbal remedies will present the manufacturers of these products, in terms of bioavailability, phytoequivalence, standardization and other quality control, and the performance of properly designed clinical trials leading to the introduction of new phytomedicines. In the US, the passage of the Dietary Supplement Health and Education Act in 1994 led to the categorization of herbal medicines as "dietary supplements" for "health maintenance", and has resulted in the influx of hundreds of new plant products onto the shelves of pharmacies and health food stores (Robbers & Tyler 1999). Many of these products have not been studied comprehensively, and are often of incompletely known chemical composition and/or pharmacodynamic activity, and there are sometimes concerns about their quality or potential interactions when co-administered with prescription drugs. This is in sharp contrast to the thoroughness in which single-agent synthetic or natural product therapeutic drugs must be evaluated before receiving approval by the US FDA. Perhaps the present state of affairs with regard to these new botanical dietary supplements is more in keeping with the situation which might have been expected at the turn of the 20th century than at the present

time. Hence, there are numerous opportunities for those in academic and other institutions to perform highly socially relevant research on these products, not only in the field of pharmacognosy, but in the pharmaceutical sciences as a whole. The outlook for those wishing to perform such research in the US is particularly auspicious due to the recent inauguration of a new funding agency at the National Institutes of Health, namely, the National Center for Complementary and Alternative Medicine.

Conclusions

As we enter the 21st century and the new millennium, it may be argued that interest in pharmacognosy as a discipline and natural products in general is at an all-time high. The last decade has seen a greater use of botanical products among members of the general public through self-selection than ever before. This phenomenon has been mirrored by an increasing attention to herbal remedies (phytomedicines) as a form of alternative therapy by the health professions inclusive of pharmacy and medicine. The major new addition of herbal remedies to pharmacy practice has greatly increased the relevance of pharmacognosy as a didactic subject, and has augmented interest in this topic among pharmacy students. While pharmacognosy has always remained as a strong core discipline in the professional pharmacy curriculum in certain countries, it is not unreasonable to suggest that **every** school or department of pharmacy in future should have **at least one faculty member** who is thoroughly knowledgeable in the subject of herbal remedies. The various topics and scientific approaches to research in pharmacognosy and natural products continue to expand. As interest in the scientific components of natural drugs and foods increases in both the scientific community and the general public, there will be increased funding opportunities, but there will also be increased competition from those in disciplines outside of academic pharmacy institutions to perform this sort of research. Though pharmacognosists have valuable knowledge that can be extremely useful in natural products drug discovery efforts, these sorts of projects can be envisaged as becoming much more complex in the future, with an increasing number of scientific disciplines represented. It is to be hoped that as research in pharmacognosy becomes ever more specialized, the present strong and unified representation at international and national pharmacognosy meetings does not become fragmented. Young pharmacists and graduates with degrees in other science disciplines who are interested in entering a research career in pharmacognosy or natural products work should aim to have as broad a background as possible, and should gain an understanding of new developments that come to the fore, such as combinatorial biosynthesis, genomics, and proteomics. More flexibility will be required of new researchers of natural products than ever before, but because of the new tools available, the rewards in terms of inherent interest and the contribution to society will be correspondingly greater than they have ever been previously. There seems little question that pharmacognosy as a discipline will have a role to play for many more years, and that pharmacognosists can look to the future with a great deal of anticipation.

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