

Natural products



Photograph courtesy of Macfarlan Smith Ltd

Galanthus woronowii (daffodil); source of galanthamine

plants as a source of new medicines

Putting aside the excitement surrounding the human genome, in the near future we may well start to see the emergence of a new class of prescription medicine containing complex mixtures of plant extracts. This article discusses the important role that plants can play in the search for new medicines and effective therapies.

By Jennie Gwynn and Peter J Hylands

As technology advances, the pharmaceutical industry is increasingly focusing on the human genome as a source of the many unanswered questions relating to how disease is prevented, diagnosed and treated. It is easy to forget one of the other life forms that has contributed much to our current understanding of medicine and many effective therapies. Plants are an abundant natural source of potential new medicines and as a pharmaceutical company seeks to achieve an optimally balanced R&D portfolio this potential should be kept in mind as a target for new or additional funding. In assessing the potential risks and benefits associated with such investment some insight into the following should contribute to decision making:

- historical evidence
- current research trends
- future opportunities
- development issues
- regulatory hurdles
- facilitative technologies
- market potential and competition

What contribution have plants made to medicine today?

Prior to the advances in synthetic chemistry and the discovery of antimicrobials in the late 19th early

20th centuries, plants provided the major source of medicines. Evidence of their use as long as 50,000 years ago comes from the Middle Eastern grave site of a Neanderthal man containing plant specimens, seven of which are still in use medicinally today by the local population¹.

The hugely diverse plant kingdom, consisting of some 250,000-300,000 species, continues to evolve and adapt to a multiplicity of environmental conditions and to protect from pathogens and predators. Whether by serendipity or design the human species appears, in contrast, to have stabilised its genetic code. Many characterised human endogenous receptors, important in physiological function, are activated by plant-derived chemicals; for example the opioid, and the more recently discovered cannabinoid, receptors. It is not unreasonable to hypothesise that many more structure-activity relationships, of physiological and pharmacological significance, involving plant molecules have yet to be characterised.

In excess of 20% of the ethical turnover of pharmaceutical companies today is generated from plant-derived medicinal products. Some of these are the original natural product, others the synthetic equivalent or synthetic derivatives designed to improve efficacy or decrease associated side effects. The most important of these, representing historically accepted medical practice, yet still prescribed today, are listed in

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Artemisia annua; source of artemisinin

Photograph courtesy of High Value Horticulture Ltd

Table 1. More recent new product introductions and some plant-derived products currently in development are included in **Table 2**.

Another area of interest in the West is herbal medicine, which has proved extremely popular in some continental European countries with many products licensed as medicines, and is growing in significance in the UK and the US as herbal remedies, nutraceuticals or functional foods. The application of herbal medicine goes back centuries in Traditional Chinese, Ayurvedic, Unani and other cultures in the developing world. Thousands of plants are used as a basis for these traditional practices of medicine and while many in the West are sceptical of any therapeutic value, more and more beneficial effects are being demonstrated. A number of new companies have begun to focus on plant-derived medicines with a number of products, some new others derived from traditional medicine, already being investigated in clinical trials.

How can future opportunities be derived from traditional medicine?

The accumulated evidence derived from centuries of use in traditional medicine or from knowledge of how species of plants have evolved and adapted to their environment can substantially reduce the time to identify development candidates. Thousands of plant-derived products have been prescribed for patients by practitioners of traditional medicine for centuries, providing supporting, although often only anecdotal, evidence of potential efficacy and lack of frank toxicity. These data are becoming more accessible in today's world of advanced communication, informa-

tion technology and improvements in global standards of education and welfare.

Scientists and clinicians in the Far East and Asia, many trained in the West, are applying Western clinical research and practice to traditional products and publishing their results in reputable, peer reviewed, journals. Further significant preclinical and clinical research is published in original language journals but is becoming more easily available from databases like Medline. Some of the newer companies involved in phytopharmaceuticals have specialist internal staff and/or have established links with companies, experts and academic institutions in the countries used to source materials. All these avenues can facilitate narrowing the search for potentially effective medicinal plants.

Manufacturing plant recently commissioned at Macfarlan Smith to process and extract galanthamine from *Galanthus woronowii*



Photograph courtesy of Macfarlan Smith Ltd, manufacturers of alkaloids and fine chemicals

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Table 2
Some more recent new products and drugs in development

SOURCE PLANT	PLANT PRODUCT*	DERIVATIVE*	INDICATIONS	MODE OF ACTION
<i>Galanthus woronowii</i>	galanthamine (Shire/Johnson & Johnson)		Alzheimer's	reversible cholinesterase inhibitor
<i>Podophyllum peltatum</i>	podophyllotoxin	etoposide (Bristol Myers Squibb/Novartis)	anti-cancer	topoisomerase II inhibitor
<i>Camptotheca acuminata</i>	camptothecin	topotecan (SmithKline Beecham) irinotecan (Pharmacia/ Aventis)	anti-cancer	topoisomerase I inhibitor
<i>Artemisia annua</i>	artemisinin	artemether (Aventis)	malaria	schizontocide
<i>Taxus brevifolia</i>	taxol (Bristol Myers Squibb)	docetaxel (Aventis)	anti-cancer	microtubule disaggregation inhibitor
<i>Tricosanthes kirilowii</i>	tricosanthin		anti-cancer	reverse transcriptase inhibitor
<i>Coleus forskolii</i>		forskolin	anti-viral glaucoma impotence	adenylate cyclase stimulator
<i>Cannabis sativa</i>	Δ^9 -tetrahydrocannabinol (Unimed) cannabidiol	nabilone (Eli Lilly) Δ^9 -tetrahydrocannabinol hemisuccinate	antiemetic in chemotherapy appetite stimulation multiple sclerosis spasticity pain management	analgesic sedative muscle relaxant
<i>Silybum marianum</i>	silymarin (Madaus)		hepatic disorders amanita poisoning	free radical scavenger

* = company affiliation denotes marketed product. Source: various, see additional source material

Table 1
Significant plant-derived pharmaceutical products

SOURCE PLANT	DRUG	INDICATION
<i>Salix spp</i>	aspirin	analgesic anti-pyretic
<i>Atropa belladonna</i>	atropine	cardiovascular anti-cholinergic pupil dilation
<i>Digitalis lanata</i>	digoxin	cardiotonic
<i>Mucuna deeringiana</i>	(L)-dopa	anti-parkinsonism
<i>Dioscorea deltoidea</i>	diosgenin	anti-fertility
<i>Papaver somniferum</i>	morphine codeine	analgesic and antitussive
<i>Colchicum autumnale</i>	colchicine	anti-tumour anti-gout
<i>Cinchona ledgeriana</i>	quinine	anti-malarial
<i>Catharanthus roseus</i>	vincristine vinblastine	anti-tumour

Source: various, see additional source material

The demands and expectations of the increasingly knowledgeable, health conscious and environmentally aware consumers and patients of the Western world are placing increasing pressure on regulators, clinicians and politicians. A recent example of where this

has made an impact, is in the pressure to recognise the medicinal qualities of the plant *Cannabis sativa*. While the psychotropic properties of cannabis are well recognised and the therapeutic effect of its major component Δ^9 -tetrahydrocannabinol in alleviating nausea and vomiting caused by chemotherapy has been proven, evidence of efficacy in other diseases like multiple sclerosis, while compelling is mainly anecdotal. There now exists, however, a vast database of research on cannabis, its individual components and synthetic derivatives. Relatively recently, endogenous cannabinoid receptors were identified in man and animals, opening up a new field of research into cannabinoid receptor agonists and antagonists². Compounds synthesised by companies in the past, shelved or abandoned because of the associated stigma, may well be resurrected or utilised to refine the search for more specific targeted candidates.

While the stigma of abuse is not associated with traditional ethnic medicines an element of quackery is sometimes applied to it by the so-called educated West. It should not be forgotten, however, that much of our current understanding of medicine is based on the discovery of the medical application of plant-derived substances like opium, curare, atropine and ephedrine. More credence today is being given to the activity of herbs like St John's Wort, Saw Palmetto and



Papaver somniferum
(opium poppy); source of
morphine and codeine

Photograph courtesy of Macfarlan Smith Ltd

Ginkgo biloba. Table 3 lists some of the current most popular medicinal herbs. Increasing use of some of these active agents is leading to a greater incidence of adverse events, often due to interactions with prescription drugs. Clinical awareness of the potential for these types of interactions has led to a number of studies which have recently been published³, prompting regulatory authorities to issue guidance on the use of some products. While this could be viewed negatively for herbal products it does, however, serve to show that many herbs can produce significant pharmacological effects and supports the developing view that their use requires improved regulation and control.

During the 1990s some futurists and more recently pharmaceutical scientists, including Dr George Poste⁴, have predicted that one of the major advances in the next couple of decades will be the individualisation of therapy. This proposal has been linked mainly to the advances in genomics. For many hundreds if not thousands of years, however, some ethnic cultures have been individualising treatments for patients. Two important examples utilising plant-derived medicines, come from China – Traditional Chinese Medicine, and India – Ayurvedic Medicine. Thousands of herbs have been associated with beneficial effects that are often given in multiple combinations designed by practitioners for each individual patient's total well-being.

More recently academic researchers have investigated pharmacological activity for many of the more widely used herbs, utilising methods accepted by Western cultures. For example, many herbal products available in China for the treatment of benign prostatic hypertrophy are now being screened for their activity in mice with testosterone-induced hyperplasia, a

classic test for alpha reductase inhibition⁵. An extract of the plant *Serenoa repens* has been shown to be more effective and associated with fewer side effects than finasteride⁶. This has contributed to a growing interest in the use of and developing herbs as potential new medicines in the Western world. A significant example of this is the development of a Chinese herbal mixture for the treatment of eczema by Phytopharm Plc, based on the observation that a patient receiving treatment from a TCM practitioner in London was showing unexpected signs of significant improvement. Some examples of the many INDs currently with the FDA are listed in Table 4⁷.

Table 3
Some of the current most popular botanical medicines

LATIN NAME	COMMON NAME	ACTIVITY
<i>Ginkgo biloba</i>	gingko	stimulation of peripheral circulation
<i>Echinacea</i> spp	coneflower	immunostimulant
<i>Allium sativum</i>	garlic	cholesterol reducing
<i>Serenoa repens</i>	saw palmetto	alleviation of symptoms of BPH
<i>Panax ginseng</i>	ginseng	'tonic'
<i>Tanacetum parthenium</i>	feverfew	migraine prophylaxis
<i>Hypericum perforatum</i>	St John's Wort	anti-depressant
<i>Crataegus</i> spp	hawthorn	cardiotonic, hypotensive
<i>Ephedra</i> spp	ma huang	CNS stimulant, appetite suppressant
<i>Valeriana officinalis</i>	valerian	calmative, sleep inducing

Source: ten Kate, K and Laird, SA 1999

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Table 4
Some examples of herbal-based INDs
currently with the FDA

HERB	INDICATION
St John's Wort	depression
Ginkgo biloba	cognitive impairment
Saw Palmetto	benign prostatic hypertrophy
Green Tea	cancer
Chinese Herb Formula	menopausal hot flushes
Chinese Herb Formula	plantar warts
Chinese Herb Formula	eczema

Source: Proceedings of Herbal Extracts 2000; citation: FDC Reports, May 1998

References

- 1 Fowler, MW. Plants, Pharmaceuticals and Plant Cell Culture – A Perspective, In: Recontrés Europeane de Phytochimie. Actes du Colloque (eds Brunetton, J and Guinandau, H) Angers, France, 124-133, 1993.
- 2 Pertwee, RG. Neuropharmacology and therapeutic potential of cannabinoids. *Addiction Biology* 5, 37-46, 2000.
- 3 Fugh-Berman, A. Herb-drug interactions. *Lancet*, 355, 134-38, 2000.
- 4 Poste, G. The right treatment for the right patient. *Scrip Magazine*, January 2000, Issue 86, PJB Publications Ltd, UK, 2000.
- 5 Yu, H. Personal communication. Oxford Natural Products plc. March 2, 2000.
- 6 Champault, G, Patel, JC and Bonnard, AM. A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. *British Journal of Clinical Pharmacology*, 18, 461-462, 1984.
- 7 Proceedings from Herbal Extracts 2000 Feb 24-25, London. IBC Global Conferences Ltd.

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Regulatory issues for licensing of plant-derived medicines and how are they evolving?

This is not to say that the development of plant-derived medicines is without complication. The key issues for development programmes, where it proves difficult or for other reasons not desirable to synthesise the active plant component(s), relate to identification, standardisation and consistency of material. Fears of adulteration or even contamination of plant material by potentially toxic materials are not unfounded and serve to substantiate the long standing attitude of regulators towards combination products and a frank 'adverse reaction' to complex mixtures like herbal extracts. As a result many companies have shied away from this potentially fruitful area of R&D.

It is reassuring for those interested in developing plant-derived medicines that the anticancer taxol has been so therapeutically, and commercially, successful. The recent first European approval of galanthamine for Alzheimer's disease in Sweden further supports the premise that plants are a source of new medicines.

Major initiatives have been under way in Europe and the US for some time to address the regulation of herbal medicines. This is mainly in recognition of a lack of continuity of, or complete absence of regulation, for herbal products used as medicines, nutraceuticals and functional foods and of consumers' desire for access to such products. In the US the final rule relating to the DSHEA regulations has recently been published (Federal Register, 6th January 2000). This relates to statements that can be made about the effects of dietary supplements on bodily structure or function and is of major significance to manufacturers of herbal products targeted at the general consumer. Europe is not as advanced in this specific area of regulation but the European Agency for the Evaluation of Medicinal Products has made significant progress towards achieving a European-wide assessment of herbal medicinal products including evaluation of monographs for well recognised herbs.

While regulatory approval of some of the more widely known medicinal herbs is potentially being made easier, that of new chemical entities remains as stringent as ever. New plant-derived chemicals, extracts and their derivatives fall within the latter category. Some phytopharmaceutical companies are focusing their efforts on single molecules or plant extracts with the aim of simplifying the regulatory process by avoiding complex mixtures and combinations. Others are looking to the future success of their new technologies to facilitate approval.

How will new technologies facilitate product licence approval?

To overcome the major regulatory concern related to quality of plant-derived material, a few companies specialising in phytopharmaceuticals, including PharmaPrint, CV Technologies and Oxford Natural Products, are independently developing and patenting new technologies. Some of these technologies are addressing the agricultural process and practice leading to raw materials of consistent source, quality and yield; essentially to facilitate Good Agricultural Practice. It is worth noting in this context that the ability of developing countries and the emerging nations to pay for expensive new medicines is in part influenced by their infrastructure and economic growth. Sourcing of plant materials from their natural habitat, grown under controlled conditions, can contribute to local economies and to provision of better quality lower priced medicines. In addition this can contribute to the conservation of rare species and to the obligations laid down by The Convention on Biological Diversity.

Others of these new technologies are combining advanced chemical and biological assays that will enable the raw material to be identified and standardised in order to meet the stringent regulatory requirements for quality. It is of relevance to note that PharmaPrint Inc has recently been granted a US patent for the application of its PharmaPrint process technology for saw palmetto, a product that they are investigating under an IND for benign prostatic hypertrophy. These new technologies, if ultimately successful in their application, will not only facilitate regulatory approval of a new generation of safe and effective products containing unique, 'fingerprinted' plant extracts but also afford a greater degree of product exclusivity and protection of both intellectual property and investment.

Where can acquisitions to add to the R&D portfolio be found?

Many herbal product companies are taking advantage of the new DSHEA regulations in the US for nutraceuticals and exploiting ways of suggesting that the quality of their products is better than their competitors. Some of the multinational pharmaceutical companies, with a major interest in consumer products, are establishing links with herbal product companies and capitalising on the growing consumer interest in herbal remedies and their environmentally friendly or 'green' association. This is a significant and growing market but is still dwarfed by prescription pharmaceuticals.

Some of the multinationals have natural product R&D programmes that have been in existence for a

considerable number of years where the focus is broader than plants or has actually moved away from plants as a source of new medicines in recent years. Where large screening programmes are in place there is the opportunity to adapt and take advantage of the increasing database of information on plants. Many companies today, however, are streamlining their internal R&D organisations and seeking licensing opportunities from outside. It would seem prudent, therefore, to maintain a watching brief on the proliferating number of small companies specialising in plant-derived medicines. Not only do these companies have the relevant internal expertise to identify significant leads; they recognise and understand the issues associated with developing plant-derived medicines. Access to their new technologies should enable, in the shorter term, development of safe and effective plant-derived medicines of high and consistent quality.

In the near future, we may well start to see the emergence of a new class of prescription medicine, containing complex mixtures of plant extracts designed, or inherently containing the active synergistic components, to cure disease, treat associated symptoms and prevent recurrence. **DDW**

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Additional source material

- Clark, AM. Natural Products as a Resource for New Drugs. *Pharmaceutical Research*, 13 (8), 1133 – 1141, 1996.
- Grabley, S and Thiericke, R. Bioactive agents from Natural Sources: Trends in Discovery and Application, *Advances in Biochemical Engineering/Biotechnology*, 64, 101 – 154, 1999.
- Harvey, AL. Medicines from nature: Are natural products still relevant to drug discovery? *Trends in Pharmacological Sciences*, 20 (5), 196 – 198, 1999.
- ten Kate, K and Laird, SA. The Commercial Use of Biodiversity: Access to genetic resources and benefit sharing. Earthscan Publications Ltd, 1999.
- Xu, G. Chinese Herbal Medicine, A practical guide to the healing power of herbs. Vermilion, UK, 1996.
- Cannabis: The Scientific and Medical Evidence, 1998, Select Committee on Science and Technology, House of Lords, Session 1997-98, 9th Report. London: The Stationery Office.
- Botanical Medicine: Efficacy, Quality Assurance, and Regulation. Eskinazi, D (ed), Mary Ann Liebert, Inc, USA, 1999.
- Martindale: The complete drug reference, 32nd edition. Kathleen Parfitt (ed). The Pharmaceutical Press, 1999.

Websites

- www.herbtech.com (CV Technologies Inc)
- www.oxfordnaturalproducts.com
- www.paracelsian.com
- www.pharmaprint.com
- www.phytera.com
- www.phytopharm.co.uk