Review
Plants, medicines and man

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Abstract: Plants have long been a source of therapeutic agents used by man. Some 80% of the world's population still rely upon plants for primary health care; even today in Western medicine, and despite progress in synthetic chemistry, some 25% of prescription medicines are still derived either directly or indirectly from plants. The use of plants in medicines ranges from crude preparations or extracts, to refined extracts and single molecular species. In terms of categories of use this encompasses food supplements, herbal medicines, botanical drugs and prescription medicines. Increased interest in plants as a source of novel pharmacophores recognizes their chemical diversity and versatility, not matched by synthetic chemistry libraries. In spite of the surge of activity in synthetic chemistry over the last 20 years or so, almost half the some 850 small molecules introduced as drugs were derived from plant sources. Over 100 small molecules derived either directly or indirectly from plants are currently at some point in the clinical trials process. It is argued that the present use of plant-derived drugs and remedies only scratches the surface of what is a major reservoir of untapped potential, the level of biological and chemical diversity possessed by plants having much to offer in the drive for novel therapeutic agents in the fight against disease. Additionally novel developments in plant biotechnology and molecular biology add further dimensions to the use of plants in the production of therapeutic agents.

Keywords: plants; phytomedicines; herbal remedies; botanical drugs; plant-based prescription medicines; chemical diversity; biodiversity

INTRODUCTION

For millennia man has utilized the properties of plants not just for food and shelter but also for health and well-being. Herbal extracts and preparations, for a long time the mainstay of the healer and physician's 'tool kit', still comprise the major part of primary health care for some 75–90% of the world's rural population;[1] even in relation to Western medicine, plants still provide the basic raw materials for some 25% of prescription drugs.[2] After the ascendancy of synthetic chemistry over natural product drug discovery and development during the latter part of the 20th century there are signs of a reawakening of interest in the sector, with the pharmaceutical industry once again beginning to look at the plant kingdom as a source of chemical scaffolds for drug synthesis, often coupled to highly innovative molecular approaches seen in many of the small biopharmaceutical companies.[3] Coupled to the sometimes stunning advances in molecular biology and genetic engineering, plants are also increasingly seen as potential 'factories' for the production of a wide range of high-value therapeutic agents. It is the purpose of this mini-review to try to capture something of the nature of these developments and the possible renaissance of the triangle; plants, medicines and man.

The mini-review begins by seeking to place in a historical context the use of plants by man as a source of medicines, illustrating the potentials and depth of resources available for novel medicine discovery from plants. It moves on to look at the different categories of herbal remedies and drugs, focusing particularly on plant-derived prescription drugs, but also mentioning on the way the relatively newly recognized – for the USA and UK at least – regulatory category of botanical drugs, before revisiting the plant kingdom as a source of molecules for new drug leads. Finally it gives passing consideration to some of the potential impacts of recent developments in plant biotechnology on pharmaceutical production.

FROM PAST TO PRESENT

50 000 years ago the body of a Neanderthal man was laid to rest in a cave (the Shanidar Cave) on the border of northern Iraq and Iran. Around the body were placed eight different species of herbs, all of which we now know to possess medicinal properties. Of those eight herbs, seven are still found growing in the same locality today, and one of them, *Ephedra*, gave us the potent bronchodilator ephedrine, today a prescription (Rx) medicine but now produced through chemical synthesis.

The discovery of the grave with its herbal treasures has provided one of the earliest indications of the importance of plants to man as a source of therapeutic

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remedies. Down the millennia the use of a wide variety of plants by humans to satisfy a range of therapeutic needs grew. Recorded history provides reference to the use of medicinal plants from many parts of the world, as far apart as China, Greece, India, Rome and the Middle East. The use of medicinal plants was particularly well developed in China. One of the earliest known Chinese herbalists, Shen Nung, who lived around 2800 BC, described some 350 medicinal or herbal plants. Sumerian ideograms from around 2500 BC provide a detailed account of a wide range of herbs used for their medicinal properties, and are noteworthy for mention of the opium poppy, still the source of one of the most powerful analgesics in the pharmaceutical armamentarium today, but at that time called the 'plant of joy', indicating a perhaps rather different use! A particularly detailed and extensive record was produced under the direction of Hammurabi, King of Babylonia from 1728 to 1686 BC. Known as the Code of Hammurabi, the records contained many herbal remedies that we recognize today, and are remarkable for their detail. That there was an early trade in medicinal plants is to be seen from the descriptions of medicinal plants from Syria in the temples of Karnak in Egypt dating from around 1500 BC. From India, descriptions of the use of medicinal plants were often to be found alongside poetry and verse, particularly in the Vedas of 1500–1400 BC, and there is of course evidence of extensive use of medicinal plants by the indigenous peoples of North and South America. Europe also had a foundation of Celtic herbal medicine, sadly largely lost in the mists of time.[4,5] Throughout the Middle Ages and well into the 19th century within Europe, as in other parts of the world, herbal medicines provided the mainstay of primary health care. Single-entity prescription medicines which dominate Western primary health care today began to appear in the later part of the 18th century. While the 19th century marked a steady but by no means complete transition from complex mixtures and extracts to single-substance prescription medicines, plant extracts and botanically derived drugs continued to provide the mainstay of the general physician's armamentarium well into the 20th century.

The transition from herbal preparations to defined, single chemical entity prescription medicines is well illustrated and marked by the discovery of the cardiac glycoside digitalis from the foxglove, *Digitalis purpurea*. The use of the foxglove in the British Isles and elsewhere goes back well before recorded history, to Celtic times, perhaps 2000 years or more ago and possibly derived from earlier Druidical influence. The earliest known detailed written record of use goes back to the Physicians of Myddfai, herbal doctors who lived in South Wales as we know it today and who certainly administered to the Princes of Wales for well over a thousand years. Sometime in the 12th or 13th century these Physicians of Myddfai were persuaded to write down much of their herbal medicine knowledge. These ancient records were translated into English during the 1860s and are available for all to see, from the original Welsh texts to the English translations. In those early records or 'pharmacopoeia' foxglove is described as being used for paralysis or hemiplegia. The 'modern' story is to be picked up from about 1770, when a young Edinburgh-trained physician named William Wittering, then practising in Birmingham, fell in love with and married one of his patients who he was treating for dropsy, a painful circulatory condition. His wife told him of an old woman who lived in the county of Shropshire, close to where the Physicians of Myddfai had been active, and who used herbs to treat the condition. He visited the old herbalist, found that she used an extract of foxglove and gained the recipe from her. Wittering then set about refining the preparation, finding that there were great variations in the content of the active component in the foxglove tissues and that great care was needed to make a standard preparation which was not only efficacious but also possessed a non-lethal dose level, extracts of foxglove being quite toxic to humans if not carefully controlled and administered. (This latter situation is one which applies to many herbal remedies and preparations and which still causes concern today. It is often forgotten that plants produce some of the most potent toxins known to man, ranking with those such as snake venoms in potency and speed of action.) Following Wittering's work and that of others the active components of foxglove, digitoxin (β-methyl form) and digoxin (Fig. 1) were isolated and have since been used as the primary treatment for dropsy and a range of heart conditions. Mode of action is exclusively through action on cardiac muscle.

From Wittering's time and the identification of β-methyl digitoxin as the prime active constituent of foxglove, identification of the active component of a number of other medicinal herbs followed, including for example ephedrine from *Ehpedra*, the analgesic acetylsalicylic acid (aspirin) from willow, and the potent analgesics morphine and codeine from the opium poppy, *Papaver somniferum*. Advances in synthetic chemistry were to take the process one stage further with the use of chemical synthesis to produce such drugs rather than have them derived from plant material. Such an approach avoided the vagaries of supply and quality and has now been applied to a number of previously plant-derived drugs.

In spite of the advances of synthetic chemistry and the contribution that this has made to pharmaceuticals discovery and development during the later part of the 20th century, however, the use of herbal remedies and plant-derived drugs remains substantial and, according to recent trade statistics, is apparently growing. From a now classical study in the 1970s Farnsworth and his colleagues estimated that some 25% of all prescription medicines in the USA were plant derived at some level.[2] Similar figures have also been mentioned anecdotally in relation to use in the EU. In 2001 the WHO estimated that 11% of basic and essential drugs were 'exclusively' of flowering

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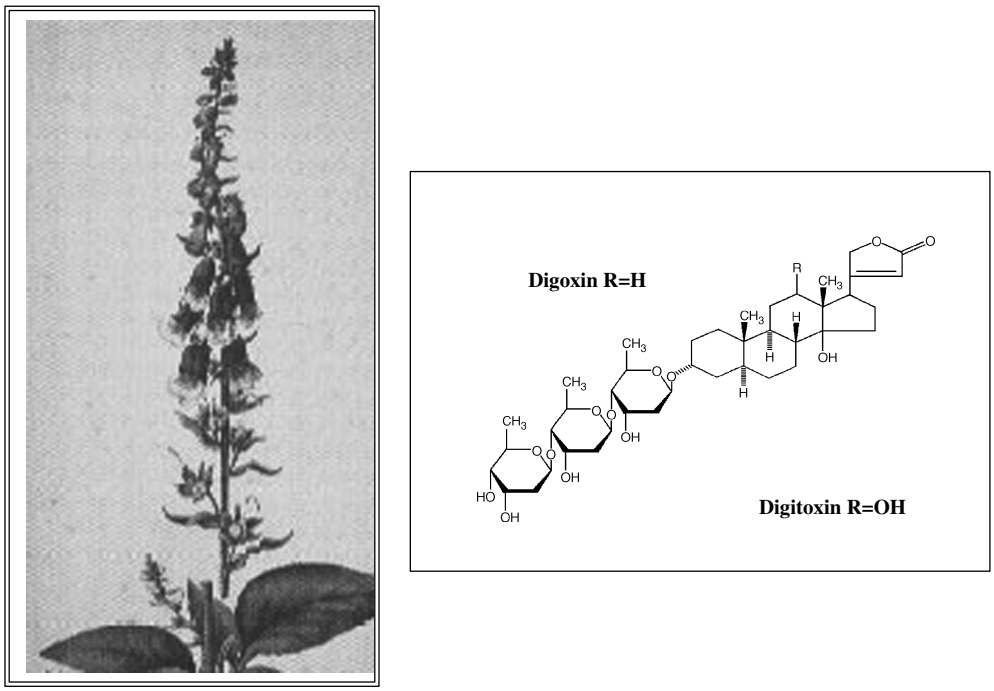

Figure 1. Foxglove (*Digitalis purpurea*) and digoxin/digitoxin.

Table 1. Examples of major drugs derived from plants[3,6,7]

Drug	Source	Pharmacological action	Chemical family
Artemisinin	*Artemisia annua*	Antimalarial	Sesquiterpene, lactone
Codeine, morphine	*Papaver somniferum*	Analgesics	Opiate alkaloids
Cocaine	*Erythroxylum coca*	Local anaesthetic	Cocaine alkaloid
Digoxin	*Digitalis pupurea*	Cardiotoinc	Steroidal glycoside
Galanthamine	*Leucojum aestivum*	Cholinesterase inhibitor	Isoquinoline alkaloid
Quinine	*Cinchona ledgeriana*	Antimalarial	Quinoline alkaloid
Taxol	*Taxus brevifolia*	Antineoplastic	Diterpene
Vincrystine, vinblastine	*Catharanthus roseus*	Antineoplastic	Bis-indole alkaloids

plant origin;[6] this corresponds to 28 major drugs. Other recent estimates suggest that 89–120 drugs are derived from plants for use in Western nations, this in turn would correspond to roughly 5–10% of the total.[7] Examples of major plant-derived drugs are shown in Table 1.

The market in plant-derived drugs was estimated to be US $20 billion in 2002, with a roughly equal split between prescription medicines and over-the-counter (OTC) preparations.[8] An indication of the current levels of growth being achieved for key groups of plant-derived chemical families which contribute the major part of the drugs in Table 1 is provided in the figures in Table 2.

The major increase seen in the use of terpenoids is probably largely due to increased use of taxol, a major anti-cancer agent, and its derivatives. Such increases as outlined in Table 2 are also to be seen in the trade levels in the raw materials for herbal medicines.[9]

Table 2. World trade figures for key plant-based drug components (billions of US dollars)[9]

Chemical family	1997	2002
Terpenoids	7.6	12.4
Glycosides	7.3	9.2
Alkaloids	3.6	4.0

The peak of interest in natural products as a source of novel pharmacologically active pharmacophores was probably during the two decades from 1960 to 1980.[7] Following that period the balance swung heavily towards synthetic chemistry libraries, which provided many of the major drugs entering prescription use in the later part of the 20th century.[3,9] A further factor was also the impact of high-throughput screening, together with the then perceived promise of combinatorial chemistry. In spite of massive investment by the pharmaceutical industry in these new technologies, the numbers of new drug leads anticipated are not there to be seen, and indeed there is increasing concern throughout the industry at the lack of druggable leads in company pipelines.

Against this backcloth there is evidence of a gradually growing renewal of interest in natural products and in particular plant sources. Such renewal of interest is based on four overlapping factors:

- indications that large pharmaceutical companies are showing interest in natural products as a source

Table 3. Plant-based therapeutics by category

Category	Nature	Example
Functional foods	Food materials often supplemented or engineered	High protein/vitamin food supplements and nutritional additives
Herbal medicines and preparations	Plant preparations with known health benefits	*Ginkgo, Echinacea*
Botanical drugs (Rx and OTC)	Standardized multi-component system	Examples in Germany (see German 'Red List);[11] others in clinical trials in UK and USA
Prescription (Rx) drugs	Single substances	Morphine, digitoxin

Rx, prescription medicines; OTC, over-the-counter medicines.

of chemical scaffolds and pharmacophore leads as their synthetic pipelines become restricted and the promise of combinatorial chemistry appears less than once anticipated;[3]
- increased consumer interest in herbal preparations towards what is often, sometimes misguidedly, regarded as 'green' and safer self-medication, coupled with what appears to be a fascination with 'traditional' medicine;
- a coming together, to a degree, of Eastern and Western medical traditions, and a recognition on the part of Western pharmaceutical companies that the traditional medicines of China, India and elsewhere may have much to offer Western medicine through leads to – and identification of – novel therapeutic agents which have been used for millennia, albeit in a somewhat different context and form;
- vastly improved technology relating to extraction systems for plant material, chemical characterization, rationalization and standardization of complex plant mixtures, coupled with improved quality, availability and reproducibility/consistency of source material.[3]

DEFINITIONS AND CATEGORIES

Therapeutic preparations from plants are derived in a variety of ways, from crude extracts of plant material, to standardized and partially purified extracts, rationalized extracts having a few defined components, and purified single chemical entities.[10] A variety of terminology exists to describe the functional use of these different preparations, often leading to confusion. The somewhat loose regulatory framework for other than Rx prescription medicines does not help the situation. The term 'phytomedicine', although used widely, is too broad in its generic meaning for this review and its use has therefore been avoided. Instead attention has been focused on four reasonably distinct categories of product/preparation which also follow in general the current regulatory regimes:

- Functional foods and nutritional additives
- Herbal medicines and preparations
- Botanical drugs
- Single chemical entities in prescription medicines

Table 3 provides examples of plant-based preparations in each of these. Only the last two of these will be considered in depth, reflecting the primary focus of this mini-review and space constraints.

Functional foods and nutritional additives

This group comprises a variety of foods and food products, all part of the new generation of 'well-being' health-related products. The group is ill defined but includes items such as anti-oxidant preparations, fruit juices fortified with calcium, folic acid preparations, cereals bred for high fibre content and so on. Such products are typically governed by food regulations and are beyond the scope of this short review. However, the level of consumer interest should not be underestimated. In recent years this has been one of the fastest-growing areas in the overall food sector. Developments in plant biotechnology and genetically engineered crops have led to much debate about the possibilities of engineered functional foods, for instance so-called golden rice for production of high levels of β-carotene as a precursor for vitamin A synthesis, and plants engineered to produce high levels of vitamins and essential oils. For a discussion of these and other aspects readers are referred to a review by Potrykus.[12]

Herbal medicines and preparations

Also often called botanical dietary supplements, the definition is again somewhat loose, and overlap occurs with functional foods above and also to a lesser degree with botanical drugs below. The distinguishing feature compared to functional foods, however, is that these are products where the aim is medical benefit, either through alleviation or prevention of some condition. The lack of precision also reflects the somewhat 'grey' status of such products in the eyes of the key regulatory bodes, in particular the USA Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA). Both organizations, however, are currently reviewing practice and regulatory structures for this group of products.[13,14] In the UK the Medicines and Healthcare products Regulatory Agency (MHRA) has recently appointed a herbal medicines advisory group, to consider amongst other things the current and potential future regulatory frameworks for such preparations[15]. At present this sector is very lightly regulated, the principal constraint being that such

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products may not be marketed with disease prevention, curative or disease detection claims. On the other hand, claims are allowed which relate to so-called structure–function relationships; i.e., such products help maintain 'normal' physiological function. A particular concern in terms of consumer protection is that no verification of safety, or for that matter efficacy, is required. It is unfortunate, as pointed out above, that the public tends to regard botanical preparations of whatever sort as 'green and friendly'. Such a view is not substantiated by published scientific evidence, and also flies in the face of the well-documented evidence that many plants and their components can be extremely toxic to humans.

As with functional foods the market in herbal medicines has shown strong growth in recent years.

Botanical drugs

Botanical drugs are well established in China, India and other Asian countries and have currency in one or two European countries such as Germany and Switzerland. They have no history of approval or use in the USA or the UK. That position has begun to change in both these countries, with botanical drugs now under detailed investigation and moving into clinical trials. The driving force behind this has been to a significant extent consumer demand for 'safer' and effective alternatives to classical prescription drugs. Four years ago the FDA published guidelines for what is essentiality a new category of botanical preparations, marked by bringing to bear a higher degree than previously of scientific rigour and standardization to what are often multifunctional as well as multi-component plant extracts.[13] This allowed marketing of these materials under the New Drug Application Approval Process (NDA).

Botanical drugs in many respects represent the interface between the medicinal systems of the East and West. Those systems of the East tend to be holistic in approach, treating the overall condition in all its complexities and interactions with a multi-component therapeutic system; in one sense, 'like with like'. In contrast, Western medicine tends to look to a magic bullet approach of single molecular species aimed at particular symptoms. There is also a philosophical difference which has major implications from a regulatory standpoint. In traditional medicine the whole multi-component preparation is viewed as the 'active', as compared again with Western medicine where the 'active 'is the single molecular species.

A number of companies in the USA and UK are now developing botanical drug products aimed at a variety of therapeutic indications. The first of these is expected to be licensed for use in the near future. Examples are presented in Table 4.

Not only is there an increasing interest in the area of botanical drugs for direct therapeutic use, but given their typically long history of use and efficacy it is increasingly recognized that they may well provide a directed drug discovery platform for novel chemistry and scaffolds in a conventional Western medicine context.

Table 4. Examples of botanical drugs under development in the UK and USA

Therapeutic target	Company
Cannabis-based preparations	GW Pharmaceuticals plc (UK)
Hepatitis c, anti-obesity, oncology	Phynova plc (UK)
Oncology, neurovascular disease	Phytoceutica Inc. (USA)
Oncology, autoimmune diseases	Phytomedica Inc. (USA)
Alzheimer's, oncology, anti-obesity	Phytopharm plc (UK)
Anti-hypertension	Ancile Pharmaceuticals Inc. (USA)

Table 5. Pharmaceuticals directly derived and utilized without modification from plants

Single substances	Chemical nature	Therapeutic effect
Atropine	Tropane alkaloid	Anticholinergic
Codeine, morphine	Opiate alkaloids	Analgesics
Taxol	Diterpene	Antineoplastic
Diosgenin	Steroid	Oral contraceptive

Single chemical entity prescription medicines

The contribution made by plant-derived drugs either directly or indirectly to the present range of drugs used in Western medicine is not to be underestimated, nor are potentials for the future (see below). Some 40–50% of current medicines are derived from natural product sources.[3,7,9] For oncology and anti-infectives the figures go higher, towards 70–80%. Of the 877 small molecules or NCEs (new chemical entities) brought to market between 1982 and 2000, 61% can be traced back directly or indirectly in origin to natural products. Of the 24 chemical scaffolds used for drug development since 1955 the great majority have a natural product and specifically plant origin.[3,7]

Three approaches to the development and use of plant-based pharmaceuticals may be discerned:

- components of plants used directly as therapeutic agents;
- semi-synthetic production from scaffolds derived from plants;
- total synthesis but where the plant-derived molecule has provided the original insight into the structure possessing therapeutic properties.

Direct use of plant components

These comprise some 6% of all prescribed drugs and cover a range of therapeutic applications from analgesics to anti-cancer agents and contraceptive preparations.[9] While in many cases alternative routes of chemical synthesis have been developed, none have provided a viable commercial alternative to direct use from the plant (Table 5).

Semi-synthetic systems
These use a core chemical scaffold derived from plants but which are modified to improve such properties as lower toxicity, greater efficacy or enhanced delivery. These comprise some 27% of all prescription drugs and, as before, are used to treat a variety of therapeutic indications.[9] Examples are shown in Table 6.

Total synthesis
These are essentially natural product mimics and comprise some 23% of natural product derived or inspired drugs.[9] Examples are provided in Table 7.

In the area of total synthesis emphasis has been to a large degree on the development of plant-based drugs for application in oncology and, to lesser extent, anti-infectives. Other sectors have not escaped interest, however, and studies are currently underway for plant-derived medicinals aimed at a range of therapeutic indications, including arthritis, anti-obesity, hypertension, pain relief, anti-infectives and diabetes.

Key to the pharmaceutical industry in its search for new pharmacophores has been the need to increase the range of chemical diversity in discovery programmes while focusing on specific therapeutic needs and the drug properties to meet those needs and aspirations. As indicated above, while much effort has been directed at this goal using synthetic and combinatorial chemistry, indications are that the diversity levels resulting from these approaches appear limited compared with those seen in plants, and also interestingly higher fungi. Some indication of the range and scale of chemical diversity to be seen in drugs derived from plants and higher fungi may be gained from the structures presented in Fig. 2, recognizing again that this merely scratches the surface of what may potentially be open to discovery programmes.

Apart from their high level of structural diversity, naturally derived structures distinguish themselves in other ways when compared to synthetic libraries; for example, they tend to have a higher degree of chirality and increased structural steric complexity compared with synthetic molecules. They also have a broader distribution of molecular activity.

It should not be forgotten that the great diversity of chemical structures observed in plants and other organisms is a result of millions of years of evolution and selection pressures resulting from interactions between the organism and its environment and challenges to the organism's survival. Many of those challenges will have been from pathogens, as still seen

Table 6. Semi-synthetic plant-derived drugs

Semi-synthetic	Chemical nature	Therapeutic effect
Taxanes	Alkaloid	Antineoplastic
Apomorphine	Alkaloid	Analgesic

Table 7. Synthetic drugs with their origin in plants

Single substances	Chemical nature	Therapeutic effect
Ephedrine	Amine	Decongestant
Salicyclic acid (aspirin)	Salicylate	Analgesic

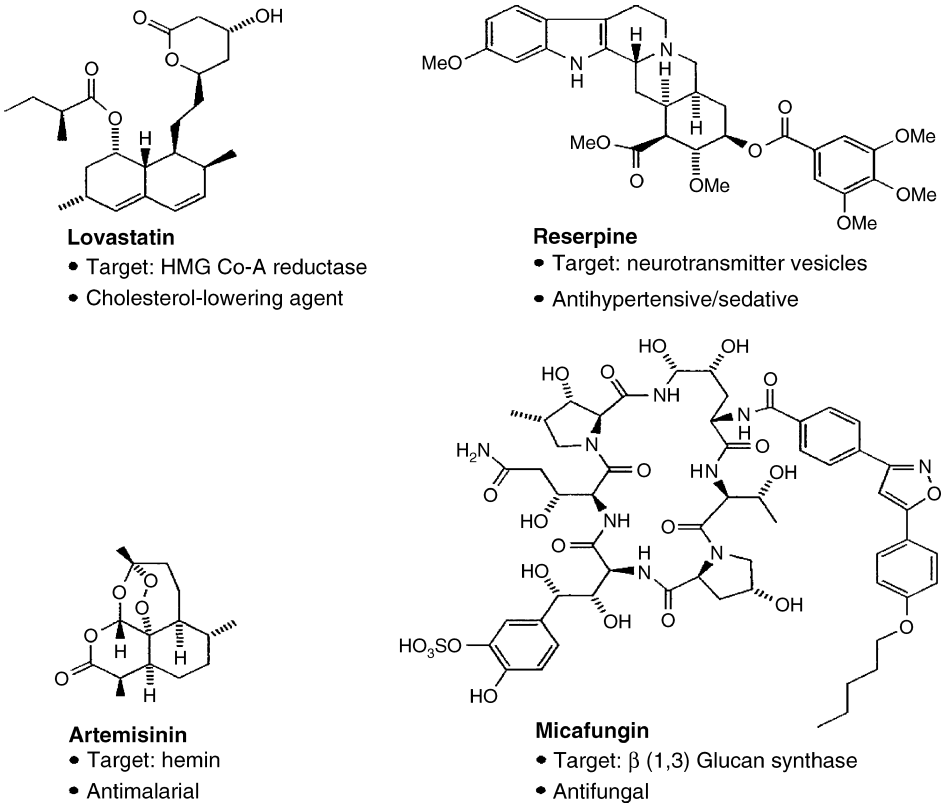

Figure 2. Examples of chemical diversity in therapeutically active natural products.[3]

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today in attack from viruses and fungi in particular. In such circumstances it is perhaps hardly surprising that plants should have developed a diverse chemistry in response to such challenges and that many structures have arisen which exhibit anti-pathogenic or in human terms therapeutic properties, from which a range of potent plant-derived drugs have been developed.

AN ALADDIN'S CAVE?

The versatility of plants in chemistry and biosynthesis is arguably unmatched by any other group of living organisms and potentially represents the most wide-ranging source of novel pharmacologically active chemical entities in the living world. While the majority of natural products used therapeutically are derived from plants, many would argue that we have as yet only scratched the surface of what may be an Aladdin's cave.[3,7] That much remains to be discovered is indicated from the areas of more traditional medicine such as those from China, South America, India and other ancient civilizations which depend upon plants for primary health care.[16] The Chinese pharmacopoeia alone contains references to over 7000 plants with medicinal properties of some form or another. Whether the emphasis will be on the development of botanical drugs and multi-component systems or the isolation and development of NCEs remains to be seen, although present indications are that it may well be a combination of both.

The Rio Earth Summit of 1992 and the accompanying Convention on Biodiversity focused attention on the alarming rate of loss of plant species from planet Earth and many were the estimates of the rate of loss of as yet unexplored plants with potential medicinal properties.[16–18] Detailed information on many of those endangered species was, and still is, lacking; conservation of this germplasm is becoming of ever-increasing priority and urgency. A little before the Rio Earth Summit, the World Health Organization held a major consultation on medicinal plants which led to the Chiang Mai Declaration (1988), in which leading authorities in the subject, international agencies including WHO, IUCN and WWF, called for recognition of the vital place of plants in both traditional medicine and modern therapies, and the need to conserve and develop that germplasm for the health and welfare of future generations.[18] Principe, in a detailed analysis of the 'value' of medicinal plants, put forward some base figures which have been little argued against and as time has moved on are often taken as yardsticks by which is measured the 'success' of conservation polices in relation to medicinal plants and their potential in the search for novel pharmaceuticals.[19] Principe argued that against a backcloth of the generally accepted figure of 250 000 plant species on the planet, by 2050 AD, i.e. some 70 years hence from his estimates, perhaps 60 000 plant species would have become extinct, roughly 25% of all plants. Many of these will be lost from the last great wildernesses of the world as industrialization and domestication creep across the landscape, and where the information base regarding plant species, phytochemistry and medical potentials is extremely sparse. Balandrina, for instance, estimated that as recently as only 20 years ago nothing was known in terms of chemistry or phytomedicine of more than 99% of the Brazilian flora. Further, the majority of potentially useful species are present in rain forests, which are under very heavy logging and environmental pressures.[20] In further analysis Principe also estimated the loss of potential drugs in terms of numbers and market value which would result from loss of species. Given the number of species which may be lost by 2050, and taking the current ratio of major drugs derived from the estimated number of investigated plant species, he suggested that possibly 60 plant species would be lost which might have been expected to provide major new pharmaceuticals to a value of perhaps $200 million (extrapolating from 1980 US dollars). Whatever the figure, this represents a not insignificant potential loss not just of products but, equally important, of potentially valuable molecules against major therapeutic need.

Moving to a level above the individual plant as a source of novel medicinals, mention was earlier made of the potentials which may exist in utilizing well-established multi-component botanical drugs from traditional medicines as a source of new chemical entities. That this approach is beginning to show potential is to be seen in the successes of the small, plant-based, drug discovery companies located in various parts of the world.

WIDER PERSPECTIVE AND FUTURE

This mini-review has focused on the production of medicinal preparations of varying degrees of refinement and in particular prescription medicines, together with the increasingly recognized possibilities for further development in the area. If the area does expand and develop as perhaps anticipated or hoped, then the major developments also seen in plant breeding, molecular biology and growth systems in recent years will have a large part to play in improving crop yields and productivities alongside greater reproducibility and consistency of raw material supplies. Particular commercial opportunities may lie ahead for those with the technology and know-how in these areas.

Underlying the great chemical diversity of plants is of course an equally diverse and versatile enzymology. Not only have major steps been made in phytochemistry in recent years, but also in the knowledge base of the underlying enzymology and pathways of biosynthesis. With the wide availability of cloning systems and vectors, the potential of discretely isolating and producing key enzymes for use in a variety of biotransformations begins to emerge into

a practical reality, making possible a combination of chemical synthesis and biosynthesis in the production of high-value molecules which in the past has not been feasible by solely chemical synthesis. Coupled with large-scale plant cell culture this may be one of the key areas for the future.[21]

Outside the scope of this review, but nonetheless needing mention for completion, is the area of molecular farming with plants and the production of high-value therapeutic proteins. Major technical advances have been made in this area in recent years and the potentials are there to be seen. Various vaccines and antibodies have already been produced from a variety of plants and the question now appears to be one more of political will, regulatory considerations and economics than technical feasibility. Excellent reviews of this area have recently been published.[22]

The signs point to an exciting future for medicinal plants, and just for once the ancient Chinese curse, 'May you live in interesting times', may have a positive element to it!

REFERENCES

1 Hamman O, The joint IUCN–WWF Plants conservation programme and its interest in medicinal plants, in *Conservation of Medicinal Plants*, ed. by Akerele A, Heywood V and Synge H. Cambridge University Press, Cambridge, pp. 13–22 (1991).

2 Farnsworth NR and Morris RW, Higher plants: the sleeping giant of drug development. *Am J Pharm Soc* **148**:46–52 (1976).

3 Koeh FE and Carter GT, The evolving role of natural products in drug discovery. *Nature Rev* **4**:206–220 (2005).

4 Plotkin MJ, Ethnomedicine past and present, in *Natural Resources and Human Health Plants of Medicinal and Nutritional Value*, ed. by Baba S, Akerele O and Kawaguchi Y. Elsevier, Amsterdam, pp. 79–86 (1992).

5 Huxley A, *Green Inheritance.* Gaia Books, London (1991).

6 Rates SMK, Plants as sources of drugs. *Toxicon* **39**:603–613 (2001).

7 Newman DJ, Cragg GM and Snader KM, Natural products as a source of new drugs over the period 1981–2002. *J Nat Prod* **66**:1002–1037 (2003).

8 Business Communications Company Ltd., *Plant Derived Drugs: Products, Technology, Applications*. B-121N. Norwalk, CT (1998).

9 International Centre for Science and High Technology. Approaches for the exploitation of biodiversity of medicinal and aromatic plants in South East Asian countries, exploring the possibility of application of combinatorial chemistry. [Online]. Available: http://www.ics.trieste.it/ActivityDetailsArchive.aspx?pcode=1.4&idx=270&activity_id=405 [31 July 2006].

10 Barnes S and Prasain J, Current progress in the use of traditional medicines and nutraceuticals. *Curr Opin Plant Biol* **8**:324–328 (2005).

11 Blumenthal M and Busse WR (eds), *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicine*. American Botanical Council, Austin, TX (1999).

12 Potrykus I, Golden rice and beyond. *Plant Physiol* **125**(1157–1161):(2001).

13 Federal Drugs Administration of the USA, [Online]. Available: http://www.fda.gov/cder/Offices/ODE_V_BRT/default.htm [31 July 2006].

14 European Medicines Evaluation Agency, [Online]. Available: www.emea.eu.int/pdfc/human/hmpc/13980004en.pdf [1 July 2006].

15 Medicines and Healthcare products Regulatory Agency (MHRA), [Online]. Available: www.mhra.gov.uk [1 July 2006].

16 Parry J, Taking a new look at an ancient tradition, *Scientist Biobusiness* **19**:39–45 (2005).

17 Glowka L, Burhenne-Guilmin F and Synge H, *A Guide to the Convention on Biological Diversity*. IUCN, Cambridge, UK (1994).

18 Akerele A, Heywood V and Synge H (eds), *Conservation of Medicinal Plants*. Cambridge University Press, Cambridge, UK (1991).

19 Principe PP, Valuing the biodiversity of medicinal plants, in *Conservation of Medicinal Plants*, ed. by Akerele A, Heywood V and Synge H. Cambridge University Press, Cambridge, UK, pp. 79–124 (1991).

20 Balandrin MF, Plant derived natural products in drug discovery and development: an overview, in *ACS Symposium Series*, Vol. 534. American Chemical Society, Washington, DC, pp. 2–12 (1993).

21 Ramachandra Rao S and Ravishankar GA, Plant cell cultures: chemical factories of secondary metabolites. *Biotechnol Adv* **20**:101–153 (2002).

22 Mascia PN and Flavell RB, Safe and acceptable strategies for producing foreign molecule in plants. *Curr Opin Plant Biol* **7**:189–195 (2004).

J Sci Food Agric **86**:1797–1804 (2006)
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