BOTANICAL PRODUCTS IN THE 21ST CENTURY: FROM WHENCE TO WHITHER?

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Abstract

Human cultures have been using botanical products for medicinal purposes since the dawn of civilisation, as with the herbal knowledge of early civilisations subsequently extending to Europe and the Middle East. Of the estimated 300,000 higher plants available today, approximately 1% are used as foods and 10-15% have a documented medical use, although few of them have withstood the scrutiny of pharmacological evaluation. In the developing world plants remain the primary sources of medicine, with more than 60% of the world's population relying on traditional medicine for their health care needs. Botanical products are used in various forms: the entire plant (or parts of it), as herbal materials (plant oils, juices or resins); or as herbal preparations (where purified or extracted compounds are mixed with other ingredients to make pills, powders, or topical preparations). While orthodox medicine uses drugs generally as single chemical entities, traditional medicine commonly uses plants as mixtures. The complexity of these mixtures poses significant challenges to the identification of active compounds and to ensuring the consistency of formulation and quality control of these preparations. This review examines some of today's uses of botanical products in Indigenous cultures, traditional medical systems, as complementary medicine and as sources of new drugs.

Human cultures have been using botanical products for medicinal purposes since the dawn of civilisation, as attested in some of the earliest written documents discovered in China, Sumeria and Egypt.[1-3] The herbal knowledge of the early civilisations has subsequently extended to Europe and the Middle East. By the 1800s, in addition to indigenous herbs, European countries also had a thriving trade in exotic medicinal plants from all over the globe.[2]

Of the estimated 300,000 higher plants available today, approximately 1% are used as foods and 10-15% have a documented medical use,[4,5] but the pharmacological properties of few of them have been thoroughly investigated.[6] In the developing world, plants remain the primary sources of medicine, with more than 60% of the world's population relying on traditional medicine for their health care needs.[7,8]

Botanical products are used in various forms: the entire plant (or parts of it), as herbal materials (plant oils, juices or resins), or as herbal preparations (where purified or extracted compounds are mixed with other ingredients to make pills, powders, or topical preparations).[9] Unlike orthodox medicine, which uses drugs generally as single chemical entities, traditional medicine commonly uses plants as mixtures, where the different components are believed to act in different ways and on different parts of the body to produce the desired effect. The complexity of these mixtures poses significant challenges to the identification of active compounds and to ensuring the consistency of formulation and quality control of these preparations.[1]

Use of herbal medicines in Indigenous cultures

Indigenous cultures have used natural remedies long before they became known to Western medicine. For example in the 17th century, Peruvian Indians were already using the *Cinchona* bark to treat malarial fevers, while the bark of the willow tree had been used to treat fever and inflammation in many traditional medical systems centuries before the active principle – aspirin – was discovered by Western medicine.[10] Indigenous cultures use medicinal plants to treat commonly occurring health problems such as infections, fever, jaundice, diarrhoea and ailments of the reproductive system.[8] Indigenous healers are more likely to recognise and treat these conditions, so their experience in treating chronic conditions such as cancer or cardiovascular diseases remains limited.[11,12] Furthermore, many cancers with a high burden of disease in the Western world (ie. cancers of the lung, colon, prostate) are less likely to be encountered in traditional cultures.[13]

Indigenous cultures likely to have discovered natural products of import to pharmacology share certain features: an ethnomedical tradition able to record this information; residence in areas with a diverse flora; and a continuity of residence in the same area over many generations.[12] Learning about the healing properties of natural products is based upon an apprenticeship system, with the information passed on orally from one generation to the next. Herbal medications are administered according to spiritual beliefs, without a standard method of identifying these plants available.[9] Until the 1980s, there was little interest in the Western world in preserving Indigenous knowledge of plants and minimal effort expended in assisting communities to preserve this knowledge.[14] Consequently, the knowledge base of indigenous plant use is slowly being eroded, as Western culture and education supersede many local traditions.[1,15] The loss of habitat in tropical forests may lead to many of the plants in use today becoming extinct in the near future, so there is an acute need to ensure species and habitat preservation and to the extent possible, to preferentially use cultivated plants in preference to harvesting them from the wild.[1,16]

Herbs in traditional medical systems

Sophisticated traditional medical systems, such as Traditional Chinese Medicine (TCM), Ayurvedha, Unani and Kampo, have a history going back for centuries, passed on to subsequent generations through regularly updated and written systems recording medical knowledge and theory.

The millennia-old TCM remains in use by the Chinese medical system today and is recognised in many other East Asian countries. While all TCMs are of natural origin, some 80% of them originate from plants, with the remainder being of animal or mineral origin.[17] To date, over 12,000 medicinal preparations from natural sources have been recorded and over 5000 have been validated as folk medicines in the Chinese traditional medical system.[4]

TCM occasionally uses single herbs (such as ginseng, gingko and ephedra), but more commonly involves multi-component herbal preparations.[17] When the isolation and characterisation of active compounds was carried out successfully, the observed effects often validated their TCM use.[1]

Some studies of Chinese medicinal herbs have confirmed a biological basis for their effect, with some inducing apoptosis, immuno-modulation, or inhibiting telomerase activity or the growth of tumours.[18,19] The evidence about the effectiveness of Chinese herbs is commonly anecdotal, rather than derived from Western style, rigorous clinical trials.[18]

A recent review of randomised clinical trials investigating TCM compounds identified 49 studies, using a comparison group, that investigated the effects of Chinese herbs in cancer treatment.[18] While overall study quality was low, the significant numbers of studies reporting positive findings suggest that Chinese herbs should remain the subject of rigorous study in cancer therapeutics.[18]

Ayurvedhic medicine describes "nourishing and rejuvenation drugs" used for longevity, memory preservation and immunomodulation, with effects mediated via the neuroendocrine axis.[20] Some plants used have complex activities. For example *Glycyrrhyza glabra* root (liquorice), commonly used for minor throat infections, also has antioxidant, chemoprotective and antimicrobial activities, while *Withania somnifera* (Ashwagandha/Indian ginseng/winter cherry) has immunomodulatory, antitumour, cytoprotective and antoxioidant properties.[21]

From traditional medical systems to Western drug discovery

The use of artemisin, derived from *Artemisin annua* (sweet wormwood, or *Qing Hao*) was first documented in TCM in 168 BC as a treatment for haemorrhoids, and since the 4th century AC as an anti-malarial,[22] but its structure was not elucidated until the mid-1970s. The drug's widespread adoption was further hampered by production challenges (as agricultural production alone was insufficient to provide the required quantities) and the highly variable concentration of the drug in plant extracts.[10]

Difficulties commonly arise in the clinical testing of a natural compound. For example, the versatility of using curcumin both as a spice (turmeric, or *Curcurma longa*) and a drug with a long history of use in Ayurvedha and TCM, makes rigorous clinical testing challenging, as the relative ease of demonstrating effectiveness in preclinical and/or pilot studies can work against the formal validation of effectiveness in rigorous randomised, placebo-controlled double blind studies. This is compounded by the fact that pharmaceutical companies have limited interest in researching a non-patentable agent and the common perception that curcurmin is more of a nutraceutical than a 'real' drug.[10]

Herbs and Western drug discovery

Ethno-pharmacology is a sophisticated approach to drug discovery, involving botany, chemistry and pharmacology, as well as many other scientific disciplines.[23] Its beginnings are credited to two French pharmacists, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou, who in 1820 extracted the active principle from the bark of several species of Cinchona and promoted the use of quinine for the treatment of malaria, thus marking the inception of a new scientific discipline.[10,24]

Historically, ethno-pharmacological information led to drug discovery in various contexts:

- Unmodified plant products where their ethnomedical use suggested efficacy for specific medical conditions ie. foxglove for the treatment of heart failure
- Products where the unmodified natural product provides some remote indication of usefulness (ie. vincristine, which was used by Indigenous cultures for the treatment of diabetes, subsequently found to be an effective anti-cancer agent)[11,25]
- Modified natural or synthetic products, based upon natural products used in folk medicine (eg. aspirin).[6,11]

After the Industrial Revolution, progress in organic chemistry led to a belief that synthetic products were going

to supplant the use of herbs and that natural remedies were relegated to use by poorly educated or lower income people and tied up with religious superstitions.[6]

The advent of synthetic organic chemistry in the 1940s and 1950s led to compound synthesis becoming increasingly popular in drug discovery.[8] With high throughput biochemical screening technologies (which are ill-suited for the screening of natural products) becoming pre-eminent,[26] many old botanical drugs were being removed from officinal compendia.[27]

Interest in natural medicines as a source of new drugs seems to be a cyclical process, with a resurgence of interest occuring in the 1970s, when many pharmaceutical companies developed active research programs into natural substances as a source of potential new drugs.[1,28]

In the 1990s, the ability to readily produce purified human enzymes and receptors tipped the balance again towards drug discovery using artificial assays (such as enzyme inhibition assays and receptor binding assays), replacing time-honoured functional assays (which measured biological activity) and this again marginalised the process of drug development from plants.[26]

It appears that even in the 21st century plants retain an important role in drug development - from 1983-1994, 65% of drugs approved for marketing were based on natural products and 50% of the best-selling pharmaceuticals in the year 2000 were still derived from natural products. [29,30]

An increased exchange of information with China has also rekindled the interest in the use of natural medicines, even in the current era of Western pharmaceutical industry domination.[2]

Furthermore, natural compounds with an identified chemical structure have provided templates for the synthesis of new pharmaceutical products, such as taxol (originally isolated from *Taxus brevifolia)*, which was converted to active analogues such as taxotere and podophyllotoxin (isolated from *Podophyllum peltatum* or *Podophyllum emodii*), which was converted semisynthetically to etoposide and teniposide.[1,13]

Advances in chemical methods, such as high performance liquid chromatography, high resolution mass spectroscopy and X-ray crystallography sped up the process of identification of chemical structures and allowed the full characterisation of these compounds, with thousands of samples now being assayed in one day in automated laboratories.[8,28]

In oncology, some drug companies focus their research on developing specific cytotoxic drugs from plants with little chemical modification, while others focus their work on identifying active principles with more specific inhibitory activities. Research marks the beginning of a lengthy medicinal chemistry process, aiming to produce a simpler molecule than the original natural compound. The new compound is ideally more potent, selective and bioavailable than the natural compound and can be produced in a cost effective manner, albeit with considerable time, effort and financial investment.[31] Some examples where natural products act as industrial intermediates include hecogenin, a steroid obtained from the juice of *Agave sisalana*, which is a synthetic intermediate for cortisone, and cortisol and cephalosporin C, obtained from *Cephalosporium acremonium*, which is the synthetic intermediate for the production of cephalosporin antibiotics.[31]

Plants as complementary and alternative medicines

The use of plants as herbal remedies remains popular in the Western world, with plants such as Echinacea, *gingko biloba*, St John's Wort and saw palmetto generating annual over the counter sales of tens of millions of US dollars in the US alone.[23] In the European Community, the sale of herbal medicinal products is worth approximately US$7 billion annually, while in the US this has increased 25 fold from 1988 to 1997, from US$200 million to US$5.1 billion.[32]

A public preference for natural products is driving the 'green consumerism' movement, leading to a substantial increase in the use of herbal remedies in the Western world.[30] In 1997, Americans' out-of-pocket expenditures on alternative therapies were conservatively estimated at US$27 billion,[33] with herbal medicines the most commonly used complementary therapies (with 38 million users).[34]

Furthermore, the perception that orthodox medicines are more likely to have adverse effects, create dependency or cause microbial resistance, and the increasing cost of Western medicine, also encourage many to choose self-medication with herbal products.[1] The increase in travel has brought about opportunities to learn more about what used to be viewed as 'exotic' cultures, many of which still have strong traditional medicine roots.[1]

In the Far East (Japan and China especially), mushrooms and mushroom extracts have been key ingredients in TCM. Three polysaccharides extracted from mushrooms (krestin, lentinan and scizophyllum) are being used in Japan in cancer therapy, alongside conventional medicine.[20] The *Ganoderma* species have a history of use in TCM dating back four millennia (*Ganoderma lucidum* is known as *reishi* or *manetake* in Japan and *Ling Zhi* in China) and are now gradually gaining recognition in the West as 'medicinal mushrooms'.[35] The active compounds of these mushrooms have demonstrated anti-cancer and immuno-modulating activities, as well as other medicinal properties relevant to cardiovascular disease, although research into their effectiveness according to Western standards of evidence, remains limited.[35,36] One of these compounds, polysaccharide K (or PSK), was isolated in 1960 and by 1987 accounted for >25% of the total national expenditure on anti-cancer drugs in Japan (where it is used in combination with conventional chemotherapy, mostly for GI cancers), so it seems that in Eastern countries at least, medicinal mushrooms have crossed the divide between traditional herbal medicine use and a pharmaceutical grade product.[35]

Future role of natural medicines

Some compounds under active investigation today have a long record of use in traditional medicine and may

provide new drug remedies for a variety of conditions. They include green tea (mentioned in ancient Japanese texts), saffron (stigmata of *Crocus sativum*), turmeric and myrrh (the dried resin of *Commiphora myrrha*, mentioned in the Bible).[3] Green tea contains epigallocatechin-3-gallate, shown to reduce the growth of some cancers in experimental animals, while myrrh, traditionally used for its anti-inflammatory effects, is being investigated for its ability to kill cancer cells resistant to other anti-cancer drugs.[3]

It could be possible that treating cancer in the future will involve a combined approach, in which Western medicine (including surgery, chemo and radiotherapy) will be used to destroy the tumour, while other treatments, such as TCM, will address the entire 'unhealthy' condition, so that a change in the body environment could facilitate cure, by addressing disease determinants more broadly and from an alternative perspective.[19]

In order to fulfill the promise of natural medicines, it is critical to adopt commonly agreed criteria for assessing their safety and effectiveness, and to ensure the sustainability of these products. This will remain of particular relevance for developing economies, where plant materials used as traditional medicines could help meet the needs of primary care medicine and lead to improvements in the quality of health care for a large proportion of the world population.[37]

In technologically advanced countries, a multidisciplinary approach to drug discovery, encompassing both the rational exploitation of natural resources and synthetic methodologies, could enhance the productivity of the drug discovery process.[38]

At the dawn of the new millennium, it was estimated that approximately 170 companies and about 40 research institutions were engaged in the process of drug discovery, evaluation and development of natural medicinal products.[39] Meanwhile, international patent applications for natural medicinal substances are increasing, drug development costs are rising and the yields from synthetic pathways in drug discovery are falling. All these factors, coupled with an ever increasing public preference for natural products, suggest that the future of natural medicinal products remains bright indeed.

References

1. Houghton PJ. The role of plants in traditional medicine and current therapy. Journal of alternative and complementary medicine (New York, N.Y 1995;1(2):131-43.
2. Phillipson JD, Anderson LA. Ethnopharmacology and Western medicine. Journal of ethnopharmacology 1989;25(1):61-72.
3. Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, et al. Natural compounds for cancer treatment and prevention. Pharmacol Res 2009;59(6):365-78.
4. Wang MW, Hao X, Chen K. Biological screening of natural products and drug innovation in China. Philosophical transactions of the Royal Society of London 2007;362(1482):1093-105.
5. Phillipson JD. Natural products as drugs. Transactions of the Royal Society of Tropical Medicine and Hygiene 1994;88 Suppl 1:S17-9.
6. Rates SM. Plants as source of drugs. Toxicon 2001;39(5):603-13.
7. Farnsworth NR, Akerele O, Bingel AS, Soejarto DD, Guo Z. Medicinal plants in therapy. Bulletin of the World Health Organization 1985;63(6):965-81.
8. Farnsworth NR. The role of ethnopharmacology in drug development. Ciba Foundation symposium 1990;154:2-11; discussion 11-21.
9. Yeung KS, Gubili J, Cassileth B. Evidence-based botanical research: applications and challenges. Hematology/oncology clinics of North America 2008;22(4):661-70, viii.
10. Corson TW, Crews CM. Molecular understanding and modern application of traditional medicines: triumphs and trials. Cell 2007;130(5):769-74.
11. Cox PA. The ethnobotanical approach to drug discovery: strengths and limitations. Ciba Foundation symposium 1994;185:25-36; discussion 36-41.
12. Cox PA. Ethnopharmacology and the search for new drugs. Ciba Foundation symposium 1990;154:40-7; discussion 47-55.
13. Cragg GM, Boyd MR, Cardellina JH, 2nd, Newman DJ, Snader KM, McCloud TG. Ethnobotany and drug discovery: the experience of the US National Cancer Institute. Ciba Foundation symposium 1994;185:178-90; discussion 90-6.
14. Baker JT, Borris RP, Carte B, Cordell GA, Soejarto DD, Cragg GM, et al. Natural product drug discovery and development: new perspectives on international collaboration. Journal of natural products 1995;58(9):1325-57.
15. Phillipson JD. 50 years of medicinal plant research - every progress in methodology is a progress in science. Planta medica 2003;69(6):491-5.
16. Soejarto DD, Fong HH, Tan GT, Zhang HJ, Ma CY, Franzblau SG, et al. Ethnobotany/ethnopharmacology and mass bioprospecting: issues on intellectual property and benefit-sharing. Journal of ethnopharmacology 2005;100(1-2):15-22.
17. Lee KH. Research and future trends in the pharmaceutical development of medicinal herbs from Chinese medicine. Public health nutrition 2000;3(4A):515-22.
18. Molassiotis A, Potrata B, Cheng KK. A systematic review of the effectiveness of Chinese herbal medication in symptom management and improvement of quality of life in adult cancer patients. Complementary therapies in medicine 2009;17(2):92-120.
19. Ruan WJ, Lai MD, Zhou JG. Anticancer effects of Chinese herbal medicine, science or myth? Journal of Zhejiang University. Science 2006;7(12):1006-14.
20. Patwardhan B, Gautam M. Botanical immunodrugs: scope and opportunities. Drug discovery today 2005;10(7):495-502.
21. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review. Altern Med Rev 2000;5(4):334-46.
22. Liu C, Zhao Y, Wang Y. Artemisinin: current state and perspectives for biotechnological production of an antimalarial drug. Applied microbiology and biotechnology 2006;72(1):11-20.
23. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environmental health perspectives 2001;109 Suppl 1:69-75.
24. Burns WR. East meets West: how China almost cured malaria. Endeavour 2008;32(3):101-6.
25. Noble RL, Beer CT, Cutts JH. Role of chance observations in chemotherapy: Vinca rosea. Ann N Y Acad Sci 1958;76(3):882-94.
26. Rishton GM. Natural products as a robust source of new drugs and drug leads: past successes and present day issues. The American journal of cardiology 2008;101(10A):43D-49D.
27. Kinghorn A. Pharmacognosy in the 21st century. The Journal of pharmacy and pharmacology 2001;53(2):135-48.
28. Borris RP. Natural products research: perspectives from a major pharmaceutical company. Journal of ethnopharmacology 1996;51(1-3):29-38.
29. Cragg GM, Newman DJ, Snader KM. Natural products in drug discovery and development. Journal of natural products 1997;60(1):52-60.
30. Schuster BG. A new integrated program for natural product development and the value of an ethnomedical approach. Journal of alternative and complementary medicine (New York, N.Y 2001;7 Suppl 1:S61-72.
31. Turner DM. Natural product source material use in the pharmaceutical industry: the Glaxo experience. Journal of ethnopharmacology 1996;51(1-3):39-43; discussion 44.
32. Mahady G. World health and international collaboration in traditional medicine and medicinal plant research. In: Eskinazi D, editor. What will influence the future of alternative medicine? A world perspective. Singapore: World Scientific Publishing Co Pte Ltd, 2001:89-104.
33. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. Jama 1998;280(18):1569-75.
34. Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997-2002. Altern Ther Health Med 2005;11(1):42-9.
35. Sullivan R, Smith JE, Rowan NJ. Medicinal mushrooms and cancer therapy: translating a traditional practice into Western medicine. Perspectives in biology and medicine 2006;49(2):159-70.
36. Normile D. Asian medicine. The new face of traditional Chinese medicine. Science (New York, N.Y 2003;299(5604):188-90.
37. Cordell GA, Colvard MD. Some thoughts on the future of ethnopharmacology. Journal of ethnopharmacology 2005;100(1-2):5-14.
38. Vuorelaa P, Leinonenb M, Saikkuc P, Tammelaa P, Rauhad JP, Wennberge T, et al. Natural products in the process of finding new drug candidates. Current medicinal chemistry 2004;11(11):1375-89.
39. Meng C. On the development of traditional Chinese Medicine in 21st century China. In: Eskinazi D, editor. What will influence the future of alternative medicine? A world perspective. Singapore: World Scientific Publishing Co Pte Ltd, 2001:23-30.