

Ayurveda and natural products drug discovery

Bhushan Patwardhan^{†,*}, Ashok D. B. Vaidya[‡] and Mukund Chorghade[#]

[†]Interdisciplinary School of Health Sciences, University of Pune, Pune 411 007, India

[‡]Bhavan's Swami Prakashananda Ayurveda Research Centre, Juhu, Mumbai 400 049, India

[#]Pharmaceutical Sciences Division, D&O Pharmachem, Inc., 14 Carlson Circle, Natick, MA 01760-4205, USA

This review attempts to portray the discovery and development of medicine from galenical to genomics, with a focus on the potential and role of ayurveda. Natural products, including plants, animals and minerals have been the basis of treatment of human diseases. Indigenous people derived therapeutic materials from thousands of plants; however discovering medicines or poisons remains a vital question. Ayurveda is a traditional Indian medicinal system being practised for thousands of years. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on ayurvedic medicinal plants. Many of the major pharmaceutical corporations have renewed their strategies in favour of natural products drug discovery and it is important to follow systems biology applications to facilitate the process. Numerous drugs have entered the international pharmacopoeia through the study of ethnopharmacology and traditional medicine. For ayurveda and other traditional medicines newer guidelines of standardization, manufacture and quality control are required. Employing a unique holistic approach, ayurvedic medicines are usually customized to an individual constitution. Traditional knowledge-driven drug development can follow a reverse pharmacology path and reduce time and cost of development. New approaches to improve and accelerate the joint drug discovery and development process are expected to take place mainly from innovation in drug target elucidation and lead structure discovery. Powerful new technologies such as automated separation techniques, high-throughput screening and combinatorial chemistry are revolutionizing drug discovery. Traditional knowledge will serve as a powerful search engine and most importantly, will greatly facilitate intentional, focused and safe natural products research to rediscover the drug discovery process.

Background

THE R&D thrust in the pharmaceutical sector is focused on development of new drugs, innovative/indigenous processes for known drugs and development of plant-based drugs through investigation of leads from the traditional systems of medicine. In addition, many nutraceuticals are being consumed in unregulated markets for perceived

benefits in health care and improvement of quality of life. Natural pharmaceuticals (Naturaceuticals), nutraceuticals and cosmeceuticals are of great importance as a reservoir of chemical diversity aimed at new drug discovery and are explored for antimicrobial, cardiovascular, immunosuppressive and anticancer drugs. Around 80% of all such products are of plant origin; their sales exceeded US\$ 65 billion in 2003. Examples of plant products and derivatives used by the pharmaceutical industry include paclitaxel, vincristine, vinblastine, artemisinin, camptothecin, podophyllotoxin, etc. The nutraceutical marketplace in Europe is estimated to be US\$ 9 billion, while the US marketplace, estimated to be US\$ 10–12 billion in 2003, is expanding at a compounded rate of more than 20% per year. The US Congress has fuelled the rapid growth of nutraceuticals with the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994. Globally, there have been efforts to monitor quality and regulate the growing business of herbal drugs and traditional medicine.

Introduction

Natural products, including plants, animals and minerals have been the basis of treatment of human diseases. History of medicine dates back practically to the existence of human civilization. The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies. The history of medicine includes many ludicrous therapies. Nevertheless, ancient wisdom has been the basis of modern medicine and will remain as one important source of future medicine and therapeutics. The future of natural products drug discovery will be more holistic, personalized and involve wise use of ancient and modern therapeutic skills in a complementary manner so that maximum benefits can be accrued to the patients and the community¹.

The Greek physician Galen (AD 129–200) devised the first pharmacopoeia describing the appearance, properties and use of many plants of his time. The foundations of the modern pharmaceutical industry were laid when techniques were developed to produce synthetic replacements for many of the medicines that had been derived from the forest. Natural products chemistry actually began with the

*For correspondence. (e-mail: bhushan@unipune.ernet.in)

work of Serturmer, who first isolated morphine from opium. This, in turn, was obtained from opium poppy (*Papaver somniferum*) by processes that have been used for over 5000 years. Many such similar developments followed. Quinine from cinchona tree had its origin in the royal households of the South American Incas. Before the first European explorers arrived, the native people of the Americas had developed complex medical systems replete with diagnosis and treatment of physical as well as spiritual illnesses. Indigenous peoples derived medicines and poisons from thousands of plants. A review of some plants that originated from Central and South America indicates that most of them either had potentially toxic characters or were from food sources. The following are a few examples²: In the early 1500s, Indian fever bark was one of the first medicinal plants to find appreciative consumers in Europe. Taken from the cinchona tree (*Cinchona officinalis*), the bark was used as an infusion by native people of the Andes and Amazon highlands to treat fevers. Jesuit missionaries brought the bark back to Europe. By the early sixteenth century, this medicine was known as 'Jesuit fever bark', quite a transformation. The name coca (*Erythroxylum coca*) comes from an Aymara word meaning 'tree'. In Andean cultures, the leaves of the coca tree have been primarily chewed to obtain perceived benefits. From ancient times, indigenous people have added alkaline materials such as crushed seashells or burnt plant ashes to the leaves in order to accentuate the pharmacologically active moiety of coca. In 1860, a German chemist Carl Koler isolated cocaine, the chemical responsible for the biological activity. He found that cocaine could act as a local anaesthetic in eye surgery. As the years passed, scientists observed that cocaine paralyzed nerve endings responsible for transmitting pain. As a local anaesthetic, it revolutionized several surgical and dental procedures. Pot curare arrowhead poison used in the East Amazon is predominately from the species *Strychnos guianensis*. Tube curare in the West Amazon is from *Chondrodendron tomentosum*; curare in modern medicine is made from this and named as tubocurarine. The jaborandi tree (*Pilocarpus jaborandi*) secretes alkaloid-rich oil. Several substances are extracted from this aromatic oil, including the alkaloid pilocarpine, a weapon against the blinding disease, glaucoma. American Indians on the island of Guadeloupe used pineapple (*Ananas comosus*) poultices to reduce inflammation in wounds and other skin injuries, to aid digestion and to cure stomachache. In 1891, an enzyme that broke down proteins (bromelain) was isolated from the fresh juice of pineapple and was found to break down blood clots. Other pharmaceuticals that have their origin in botanicals include atropine, hyoscyne, digoxin, colchicine and emetine. Reserpine, an anti-hypertensive alkaloid (*Rauwolfia serpentina*) became available as a result of work carried out by Ciba-Geigy in India. It is pertinent to note that most of these early discoveries are mainly based on traditional

medicines; many products could act as poisons in toxic doses.

Discovering medicines or poisons?

A major problem with traditional, indigenous medicine is discovering a reliable 'living tradition' rather than relying upon second-hand accounts of their value and use. In many parts of the world the indigenous systems of medicine have almost completely broken down and disappeared. This includes mostly developed countries and some developing countries where the indigenous population has been marginalized. In others, the system is fragmented with the use of indigenous materials being limited to small tribal and geographical areas, as in many parts of Africa. In anthropological terms these are 'little traditions', while the Ayurvedic Indian and traditional Chinese systems are living 'great traditions'. Although the little traditions are an excellent repository of knowledge about medicinal and poisonous properties of botanicals, researchers have mainly exploited poisonous sources. This may be primarily because of many reasons. First, it is relatively easy to present and demonstrate poisonous characteristics of botanicals. Second, there may not be a written documentation and poisonous characters get predominance by word of mouth. Third, for an outsider, poisonous characteristics differentiate between ordinary and extraordinary material for pharmaceutical development. Fourth, a considerable time period is required to demonstrate true medicinal activities with proven safety profile. Great traditions have relatively organized database, and more exhaustive description of botanical material is available that can be tested using modern scientific methods. Ayurveda and Chinese medical systems thus have an important role in bioprospecting of new medicines.

Serendipity and synthetic dominance

Pharmaceutical research took a major leap when alongside natural products chemistry, pharmacologists, microbiologists and biochemists began to unravel the chemistry of natural processes in human, animals, plants and microorganisms. Advances in synthetic organic chemistry led to the identification of many key chemical molecules that offered more opportunities to develop novel compounds. Many new drugs emerged by this route, particularly those now being used to treat infections, infestations, cancers, ulcers, heart and blood pressure conditions. Many drugs were developed through random screening of thousands of chemicals synthesized as dye-stuffs and the like; many others resulted from serendipity (happy chance) arising from sharp-eyed observations of physicians and scientists. Examples of such drugs include sulphonamides, isoniazid, anti-psychotics, anti-histamines and penicillin. Emergence of the modern pharmaceutical industry is an

outcome of all these different activities that developed potent single molecules with highly selective activity for a wide variety of ailments. The drugs produced in many cases improved on nature, viz. a new range of local anaesthetics from cocaine avoided its dangerous effects on blood pressure; chloroquine is much less toxic than quinine. These successes and many more like them resulted in reduced interest in natural products drug discovery and many major drug companies almost neglected such divisions. Work on developing new drugs for the treatment of the world's major diseases, malaria, trypanosomiasis, filariasis, tuberculosis, schistosomiasis, leishmaniasis and amoebiasis came almost to a standstill. In addition, although botanical medications continued to be produced in every country, the clinical efficacy of these was usually not evaluated and the composition of these complex mixtures was only crudely analysed. Thus, herbal medicines became the domain of 'old wives' tales' and quack medicine, exploitation of the sick, the desperate and the gullible. Sadly, herbal medicines continued to reflect poor quality control both for materials and clinical efficacy.

Back to traditional wisdom

Lag phase for botanical medicine is now rapidly changing for a number of reasons. Problems with drug-resistant microorganisms, side effects of modern drugs, and emerging diseases where no medicines are available, have stimulated renewed interest in plants as a significant source of new medicines. Pharmaceutical scientists are experiencing difficulty in identifying new lead structures, templates and scaffolds in the finite world of chemical diversity. A number of synthetic drugs have adverse and unacceptable side effects. There have been impressive successes with botanical medicines, most notably quinghaosu, artemisinin from Chinese medicine. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on ayurvedic medicinal plants³. Numerous molecules have come out of ayurvedic experiential base, examples include rauwolfia alkaloids for hypertension, psoralens in vitiligo, holarrhena alkaloids in amoebiasis, guggulsterons as hypolipidemic agents, mucuna pruriens for Parkinson's disease, piperidines as bioavailability enhancers, baccosides in mental retention, picrosides in hepatic protection, phyllanthins as antivirals, curcumine in inflammation, withanolides, and many other steroidal lactones and glycosides as immunomodulators⁴. A whole range of chronic and difficult-to-treat diseases such as cancers, cardiovascular disease, diabetes, rheumatism and AIDS, all require new effective drugs. Most developing countries have relied and will continue to rely on traditional natural medicines due to the deterrence of high costs of modern allopathic medicines.

Current estimates indicate that about 80% of people in developing countries still rely on traditional medicine-

based largely on various species of plants and animals—for their primary healthcare. Four out of ten Americans used alternative medicine therapies in 1997; total visits to alternative medicine practitioners increased by almost 50% from 1990 and exceeded the visits to all US primary care physicians⁵. The current scope of this article prevents a comprehensive discussion of alternative and complementary medicine (CAM). Every medical system or therapy has certain advantages and limitations. Modern medicine is no exception to this⁶.

Botanical medicine: research, development and markets

Thirty per cent of the worldwide sales of drugs is based on natural products. Though recombinant proteins and peptides account for increasing sales rates, the superiority of low-molecular mass compounds in human disease therapy remains undisputed mainly due to more favourable compliance and bioavailability properties. Approaches to improve and accelerate the joint drug discovery and development process are expected to take place mainly from innovation in drug target elucidation and lead structure discovery. Therefore, the need for new concepts to generate collection of large compounds with improved structural diversity has been correctly emphasized by Grabley and Thiericke⁵. There are number of problems connected with the search for new prototype drugs of biological origin. Investigations of plants used in traditional and modern medicine in China serve as a source of inspiration and as models for the synthesis of new drugs with better therapeutic, chemical or physical properties than the original compounds⁷. The World Health Organization also has recognized the importance of traditional medicine and has been active in creating strategies, guidelines and standards for botanical medicines⁸.

Commercially, these plant-derived medicines are worth about US\$ 14 billion a year in the United States and US\$ 40 billion worldwide. Americans paid an estimated US\$ 21.2 billion for services provided by alternative medicine practitioners⁹. A 1997 survey estimated that over 12% of adults had used herbal medicine during 1996 compared with 2.5% in 1990, resulting in a business of US\$ 5.1 billion¹⁰. Lilly Research Laboratories markets several million dollars worth of vincristine and vinblastine – the periwinkle derivatives used to treat childhood leukaemia and Hodgkin's disease. The US National Cancer Institute regularly earmarks large appropriations to screen 50,000 natural substances for activity against cancer cell lines and the AIDS virus. China, Germany, India and Japan, among others, are also screening wild species for new drugs.

Proven agro-industrial technologies need to be applied to the cultivation and processing of medicinal plants and the manufacture of herbal medicines¹¹. The mass screen-

ing of plants in the search for new drugs is vastly expensive and inefficient. It would be cheaper and perhaps more productive to re-examine plant remedies described in ancient and medieval texts¹². Many higher plants produce economically important organic compounds such as oils, resins, tannins, natural rubber, gums, waxes, dyes, flavours, fragrances, pharmaceuticals and pesticides. Advances in biotechnology, particularly methods for culturing plant cells and tissues, should provide new means for the commercial processing of even rare plants and the chemicals that they produce. These new technologies will extend and enhance the usefulness of plants as renewable resources of valuable chemicals. In future, biologically active, plant-derived chemicals can be expected to play an increasingly significant role in the commercial development of new products for regulating plant growth and for insect and weed control¹³.

Some of the prominent commercial plant-derived medicinal compounds include: colchicum, colchicine, betulinic acid, camptothecin, topotecan (Hycamtin®), CPT-11 (irinotecan, Camptosar®), 9-aminocamptothecin, delta-9-tetrahydrocannabinol (dronabinol, Marinol®), beta lapachone, lapachol, podophyllotoxin, etoposide, podophyllinic acid, vinblastine (Velban®), vincristine (leurocristine, Oncovin®), vindesine (Eldisine®, Fildesine®), vinorelbine (Navelbine®), docetaxel (Taxotere®), paclitaxel (Taxol®), tubocurarine, pilocarpine, scopolamine. The ultimate goal of ethnopharmacology should be to identify drugs to alleviate human illness through a thorough analysis of plants alleged to be useful in human cultures throughout the world¹⁴.

Natural products research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs by the pharmaceutical industry. While microbial products have been the mainstay of industrial natural products discovery, in recent years phytochemistry has again become a field of active interest. Drug discovery programmes based on microbial products and phytochemicals have been discussed and contrasted¹⁵. Glaxo PLC, embarked on a programme wherein extracts and fermentation broths were screened in order to detect bioactive principles¹⁶. Many other multinationals and academic institutions have created joint research programmes for plant medicine research, for example, Virginia Polytechnic Institute, Bedrijf Geneesmiddelen Voorziening Suriname, Conservation International-Suriname, and Bristol-Myers Squibb Pharmaceutical Research Institute. Several such projects were sponsored by the federal agencies of USA. University of Chicago at Illinois, University of Mississippi, Xeenova, Ayur-Core, Inc. and Bio-Ved Pharmaceuticals represent additional examples. Indian pharmaceutical companies have launched new projects: Dabur, Zandu, Arya Vaidya, Nicholas Piramal, Lupin and Ranbaxy are few prominent examples. The Pharmaceutical Research and Development Committee (PRDC) Report of the Ministry of Chemicals, Gov-

ernment of India also underlines the importance of traditional knowledge¹⁷.

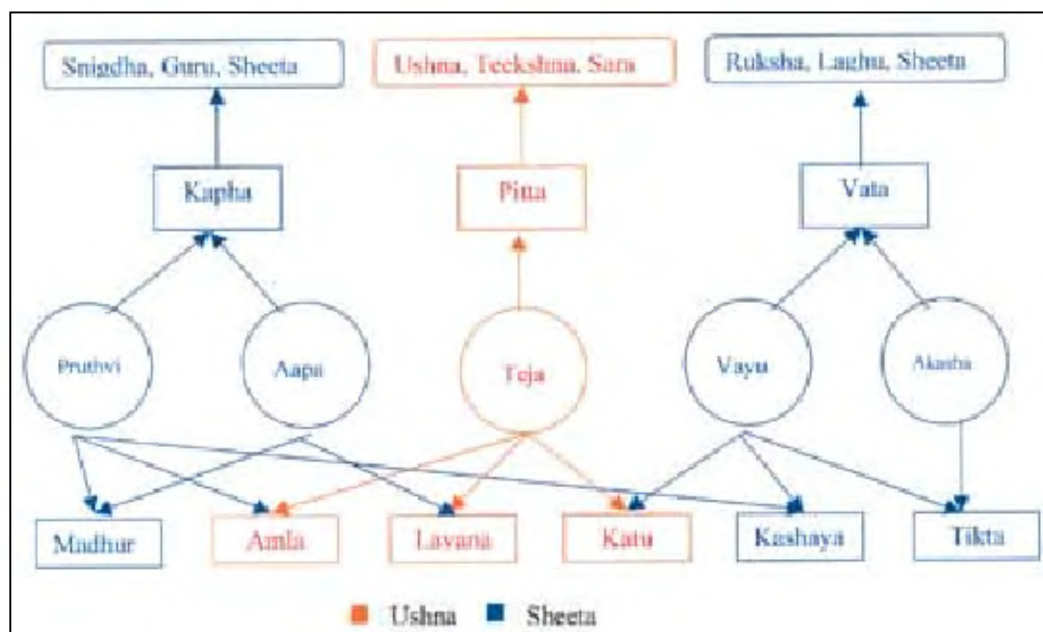
Opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products are best discussed by Clark¹⁸.

The exploration of structural chemical databases comprising a wide variety of chemotypes, in conjunction with databases on target genes and proteins, will facilitate the creation of new chemical entities through computational molecular modelling for pharmacological evaluation¹⁹.

In natural products drug discovery it is important to follow systems-theory and systems-biology applications to facilitate the process²⁰. Routine random efforts are not likely to increase the desired success rate of discovery, while experience indicates that a modified collection policy offered better chances for the discovery and development of agents for treatment of AIDS and cancer²¹. Numerous drugs have entered the international pharmacopoeia through ethnobotany and traditional medicine²². There are many similarities in traditional systems of medicine as well as ethnomedicines being connected to each other as 'great traditions and little traditions'. All botanical drugs will have to fulfil the international requirements on quality, safety and efficacy²³.

Ayurveda – the ancient science of life

Ayurveda remains one of the most ancient and yet living traditions practised widely in India, Sri Lanka and other countries and has a sound philosophical and experiential basis^{24,25}. *Atharvaveda* (around 1200 BC), *Charak Samhita* and *Sushrut Samhita*²⁶ (1000–500 BC) are the main classics that give detailed descriptions of over 700 herbs. A scholarly description of the legacy of Caraka in contemporary idiom, best attempted with a commentary from modern medicine and science viewpoint, gives some glimpses of ancient wisdom²⁷. Indian healthcare consists of medical pluralism and ayurveda still remains dominant compared to modern medicine, particularly for treatment of a variety of chronic disease conditions²⁸. India has about 45,000 plant species; medicinal properties have been assigned to several thousands. About 2000 are found in the literature; indigenous systems commonly employ about 500–700. Some recent work in drug development relates to species of *Commiphora* (used as a hypolipidaemic agent), *Picrorhiza* (which is hepatoprotective), *Bacopa* (memory enhancer), *Curcuma* (antiinflammatory) and *Asclepias* (cardiotonic)²⁹. Currently, with over 400,000 registered ayurvedic practitioners, the Government of India has formal structures to regulate quality, safety, efficacy and practice of herbal medicine³⁰. With unique holistic approach, ayurvedic medicines are usually



Summary of basic principles of ayurveda that illustrates relationship between panchamahabhoota, tridosha, rasa and gunas.

customized to an individual constitution. Exhaustive information is available in ayurvedic literature that can be converted into a large database giving information of various foods³¹, herbs, medicines and other materials with their taste, actions and utility in different disorders. An innovative method to provide quantitative representations of various ayurvedic concepts, including, Prakruti, Rasa and Guna has been developed by the Indian Institute of Chemical Technology, Hyderabad. This patented technology has been registered as Herboprint and essentially gives a three dimensional HPLC fingerprint with ayurvedic property profile³².

The ayurvedic database available in classic texts has many applications. It can be used for bioprospecting to identify new sources of medicine and to provide information about likely effects ranging from primary taste to its post-digestive effects. Information about safety, efficacy along with possible indications and contraindications is secured. Valuable information of therapeutic potential and selective benefits to people with different constitutions can be obtained. This will greatly facilitate intentional, focused and safe natural products drug discovery and development. A glimpse of ayurveda's heritage referred hitherto, is obtained from our selection of the top 20 ayurvedic drugs (Table 1). For ready reference we have given one indicative key reference for each of them. To augment this effort, we have shortlisted some broad reviews^{3,33}, database³⁴ and compendium³⁵ generally covering research on most of the popular ayurvedic drugs. We have used Medline search number of hits as an indicator. Search after giving the ayurvedic name resulted in much smaller number of hits compared to their respective

botanical names. This is mainly because similar botanicals are used and researched in different parts of the world. In case of *Curcuma*, its popular name is 'turmeric' and the ayurvedic name is rarely used. Some of the ayurvedic drugs when searched for Sanskrit names did not give any hits, which indicates potential researchable areas. In some cases, such as *Phyllanthus emblica* (earlier known as *Embllica officinalis*), the number of hits is less than that anticipated because of the recent change in its botanical name. For some drugs such as ricinus (source of castor oil), maximum hits were obtained but most of the research is related to industrial and not medicinal use. Ashwagandha remained the most researched plant drug from this list.

Herbal drug development: issues and regulations

Herbal drug development includes various steps, starting from a passport data on raw materials, correct identification, pharmacognostic and chemical quality standardization, safety and preclinical pharmacology, clinical pharmacology and randomized, controlled clinical trials. Addressing standardization is vital and needs broader consideration. Ayurvedic medicine was developed at times of limited access to technologically variable norms of standardization. The dynamic process of evolution could alter and affect the identity and structure of natural materials. For commercialization, correct identification and supply of raw material to avoid adulteration has become a challenge. Additionally, some botanical species might have been extinct. Lastly, the properties of botani-

Table 1. Top 20 ayurvedic drugs

Sl. no.	Sanskrit name	Botanical name	Main activity	Medline hit (26 June 2003)	Key references
1	Amalaki	<i>Phyllanthus emblica</i>	Rasayana	30	66
2	Ashwagandha	<i>Withania somnifera</i>	Immunomodulatory	100	67
3	Bhallataka	<i>Semecarpus anacardium</i>	Antiarthritic	36	68
4	Bilva	<i>Aegle mermelos</i>	Antidiarrhoeal	17	69
5	Chandan	<i>Santalum album</i>	Antiviral	20	70
6	Chitraka	<i>Plumbago zeylanica</i>	Antitumour	18	71
7	Dadima	<i>Punica granatum</i>	Antidiarrhoeal	41	72
8	Eranda	<i>Ricinus communis</i>	Hepatoprotective	1490	73
9	Guduchi	<i>Tinospora cordifolia</i>	Immunomodulatory	46	74
10	Haridra	<i>Curcuma longa</i>	Antimicrobial	209	75
11	Haritaki	<i>Terminalia chebula</i>	Hypolipidemic	36	76
12	Manjishtha	<i>Rubia cordifolia</i>	Antioxidant	36	77
13	Maricha	<i>Piper nigrum</i>	Bioenhancer	46	78
14	Nimba/Neem	<i>Azadirachta indica</i>	Antidiabetic	252	79
15	Pippali	<i>Piper longum</i>	Bioenhancer	26	80
16	Sariva	<i>Hemeidesmus indicus</i>	Antiulcer	15	81
17	Shunthi	<i>Zingiber officinale</i>	Antiemetic	116	82
18	Vacha	<i>Acorus calamus</i>	Psychotropic	34	83
19	Vidanga	<i>Embelia ribes</i>	Antifertility	26	84
20	Yashtimadhu	<i>Glycyrrhiza glabra</i>	Antiulcer	95	85

cals as recorded in classics may have undergone change due to time and environmental factors. Standardization of ayurvedic botanicals and medicines is required, although one cannot readily apply the typical modern pharmaceutical pharmacopoeial standards. The concept of active markers in the process of standardization needs a flexible approach in favour of the complex nature of these materials.

Recently, many international authorities and agencies, including the World Health Organization³⁶, European Agency for the Evaluation of Medicinal Products and European Scientific Cooperation of Phytomedicine³⁷, US Agency for Health Care Policy and Research³⁸, European Pharmacopoeia Commission, Department of Indian System of Medicine have started creating new mechanisms to induce and regulate quality control and standardization of botanical medicine. For ayurvedic medicine and other traditional medicines, newer guidelines of standardization are required. A botanical drug or a preparation thereof is now regarded as one active substance in its entirety, whether or not the constituents with therapeutic activity are known. This will be a major step in the development of new generation standardized botanical medicines. The WHO has published official documents on medicinal plants and WHO monographs on selected medicinal plants³⁹. Global definitions of botanical products are being developed with international cooperation and a new perspective of standardization, validation, safety and efficacy of botanical medicines is evolving – this is a good sign. Multi-component botanical formulations can be standardized with newer techniques such as DNA fingerprinting, high pressure thin layer chromatography

(HPTLC), liquid chromatography–mass spectroscopy. In-house monographs need to be evolved and critically followed. For example, a multi-component botanical formulation (Artrex) designed for the treatment of arthritis contains four botanicals and all ingredients, their respective extracts and the formulation are standardized using HPLC and HPTLC fingerprint profiles with known markers. This formulation has been granted a US patent⁴⁰. Pre-clinical studies on ayurvedic medicines are more important for validating drug safety resulting from new procedures, or extractions are used during its preparation. The value of animal testing to establish safety and toxicity is not so critical if the botanicals are used in traditional forms. Suitable animal models help in understanding the mechanism of action or pharmacodynamics of medicines. However, it is well known that no good animal models exist for some human diseases; for example, asthma, diabetes and rheumatism.

The basis of traditional medicine is in its use for a number of years and therefore its clinical existence comes as a presumption. However, for bringing more objectivity and also to confirm traditional claims, systematic clinical trials are necessary. In ayurvedic medicine research, clinical experiences, observations or available data becomes a starting point. In conventional drug research, it comes at the end. Thus, the drug discovery based on ayurveda follows a ‘reverse pharmacology’ path⁴¹. Nevertheless, all the critical pharmacopoeial tests such as dissolution time, microbial, pesticide and heavy metals contamination, etc. must be in accordance with global standards. It is important to ensure that all the ayurvedic medicine manufacture is in accordance with current good manufac-

turing procedures for herbal products^{42,43}. There have been concerns about quality standards and safety issues of herbal medicines⁴⁴. The need for new regulations for botanical medicines has also been frequently stressed and some such regulations are coming into force in different parts of the world^{45,46}.

Drug discovery: intentional not coincidental

In the sequence of their appearance, the scientific disciplines involved in drug discovery were chemistry, pharmacology, physiology, microbiology, biochemistry and molecular biology. It can be shown that new therapeutic classes of drugs like muscle relaxants; diuretics, L-dopa, antibiotics, recombinant proteins, monoclonal antibodies and others were generated on the basis of scientific opportunities rather than therapeutic need. All these drugs were created within the confines of a chemical paradigm of medicine and drug therapy. We are now witnessing the entry of a new informational paradigm into medicine that is most prominently represented by genomic sciences. This paradigm will bring two important changes in the therapy of diseases. First, molecular biology has matured to such a degree that it can now study complex genomes and their functionality in complex organisms such as humans. Therefore, results from these studies no longer have to be translated into the context of medicine: they are already within this context. Secondly, drug therapy that used to be largely symptomatic, will now aim at targets that are closer to the causes of diseases. Therapeutic progress, which used to be indirect, conjectural and coincidental, is about to become more directed, definitive and intentional. The future drug discovery will be more often based on intent rather than coincidence. Proper bioprospecting of medicinal sources will be an important factor⁴⁷.

Drug Discovery and Development Process

Expensive, time consuming, numerous bottlenecks



Economical, time sparing, least bottlenecks

Reverse Pharmacology



Reverse pharmacology helps in reducing three major bottlenecks: costs, time and toxicity.

Drug discovery, development and genomics

Opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products are discussed¹⁸. The exploration of structural chemical databases comprising a wide variety of chemotypes, in conjunction with databases on target genes and proteins, will facilitate the creation of new chemical entities through computational molecular modelling for pharmacological evaluation¹⁹. After the Human Genome Project (HGP) was launched in 1990, applications of genomics in drug discovery became more evident. Soon after the first draft of the HGP was completed, simultaneously the first biotechnology company, Genentech celebrated 25 years with number of new biotechnology products. US FDA has granted approvals to many biotechnology-based products, including Novartis: Gleevec – for treatment of CML; Genzyme: Carticel – cartilage regeneration; Immunex: Enbrel – for RA; Genentech: Herceptin – for Breast cancer; CDR Therap: Integrilin – for heart diseases; Organogenesis: Apligraf – a skin substitute. Over 300 drugs are in Phase III and over 200 are expected to be in the market by 2007.

There are many alliances, collaborations, mergers and acquisitions that have become part of the new trend in drug development. A business cooperation of US\$ 1.5 billion between Bayer and CuraGen for genetic targets of small-molecule drugs, and a Novartis and Vertex Pharma deal of US\$ 800 million for rational drug design technology, and a strategic alliance between GSK and Ranbaxy for new discovery leads sets the standards. This strategy is primarily coming from the pressing need to increase productivity and success rate of new drug discovery. The expected growth rate cannot be maintained if the present 0.5 new drug registered/annum/industry is not increased to a minimum of 3 new drugs registered/annum/industry⁴⁸.

Rediscovering drug discovery

The drug discovery process is becoming more and more complex and capital-intensive, and such companies remain 'target rich' but 'lead poor', with lead discovery as a greater bottleneck⁴⁹. In such a situation, industrialization of drug discovery process is underway. Although high-throughput screening (HTS) and combinatorial chemical synthesis are explored with great hope, general experience tells us that in most companies the investments in these technologies have not reaped rewards in new lead discovery as expected. Despite technological advances, genomics and bioinformatics predictions, actually the number of new molecular (chemical and biological) entities has dropped during the year 2002 to less than 20/year

compared to over 50/year in 1996 (ref. 50). It is estimated that to develop one successful drug, about 12–15 years and US\$ 900 million are required. The pharmaceutical industry is currently spending over US\$ 45 billion every year with about 20–25 new potential drugs and the average cost of a successful drug that enters the market is estimated to be about US\$ 5 billion per drug⁵¹. These call for systematic and critical review of methods and mindset involved in drug discovery today and indicates the need to rediscover the drug discovery process afresh⁵². The critical retrospection of the whole drug discovery process indicates that it is becoming more complex, with drugs failing at the end of the pipeline even in Phase III or Phase IV, making it more expensive and time consuming. New drug discovery must overcome such problems and become more dynamic, focused and predictive, where safety and efficacy issues are addressed along side the developmental costs. Development of new chemical/molecular entity into therapeutic drugs takes several years and is capital-intensive. The risks are also high and the success rate not good. Powerful new technologies such as HTS and combinatorial chemistry are revolutionizing drug discovery. But natural products still offer unmatched structural variety, especially as new environmental niches are explored, and their usefulness can be further extended by engineering the proteins that produce them and using them to probe biological pathways⁵³. Rediscovery of the connection between plants and health is responsible for launching a new generation of botanical therapeutics that include plant-derived pharmaceuticals, multicomponent botanical drugs, dietary supplements, functional food and plant-produced recombinant proteins. Many of these products will soon complement conventional pharmaceuticals in the treatment, prevention and diagnosis of diseases, while at the same time adding value to agriculture. Such complementation can be accelerated by developing better tools for the efficient exploration of diverse and mutually interacting arrays of phytochemicals and for the manipulation of the ability of the plant to synthesize natural products and complex proteins⁵⁴.

Many research institutions and companies together are exploring this opportunity. Biosearch Italia and Myriad Genetics have formed a drug discovery collaboration. Biosearch Italia will provide Myriad Genetics access to its natural products library. Development of activity-extract libraries will remain one of the most exciting tools to facilitate the drug discovery process. Advanced separation techniques such as SEP Box coupled with LC-MS and newer techniques like super-critical extraction will play an important role in systematic studies on natural compounds. Although in the post-genomic era we have specific information and supporting HTS systems, unfortunately the same old mindset and strategies are being continued in the drug discovery and development process. We really need a high-throughput mindset and only

technologies would not suffice. Currently, approaches to improve and accelerate the joint drug discovery and development process are expected to arise mainly from innovation in drug target elucidation and lead structure discovery. Therefore, the need for new concepts to generate the collection of large compounds with improved structural diversity has been correctly emphasized by researchers⁵.

Ayugenomics

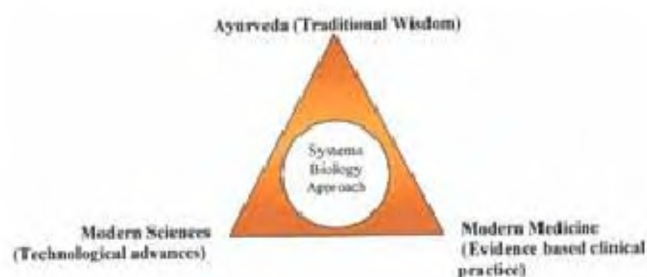
Better understanding of the human genome has helped in understanding scientific basis of individual variation. If it were not for the great variability among individuals medicine might as well be a science and not an art. After the HGP, Wilam Osler would have changed his view of medicine as an art and not as a science⁵⁵. While medical practice will continue to remain an art, medicine per se has become a science. It has become more predictive, individual and customized. For years physicians have noted these differences, but had no way to predict them. Pharmacogenetics is the study of the hereditary basis for differences in response of populations to a drug. The same dose of a drug will result in elevated plasma concentrations for some patients and low concentrations for others. Some patients will respond well to the drugs, while others will not. A drug might show adverse effects in some patients, but not in others. Populations and enzyme polymorphisms are known. Large differences among racial groups also occur for GST, an enzyme involved in detoxification of environmental toxins. These differences affect the susceptibility of individuals to various forms of cancer. CYP2D6 (a variant of the enzyme, cytochrome P450), an enzyme that metabolizes at least 30 or 40 commonly used drugs, shows great variability in individuals: some individuals are poor metabolizers, while others are rapid metabolizers. While 5–10% Blacks and Caucasians are poor metabolizers, few Asians are poor metabolizers. Ethiopians and Saudi Arabian are ultra-rapid metabolizers. Another example is phenylthiourea related taste blindness that demonstrated a chemical sensitivity to be heritable and that chemical sensitivity could serve as a means of distinguishing between individuals. African Blacks had an incidence of around 6%, American Blacks 2–23%, American Whites 30%, Chinese 6% and Eastern Eskimos 40%. All these earlier studies indicated that the differences in response to disease and drugs differ from population to population, and truly from individual to individual. The human race is believed to have originated in Africa and has 98% of the genetic make up similar to chimps. Generally speaking, humans are classified into three major groups: the Negroid, Mongoloid and Caucasoid, and genetically all are 99.9% the same. The difference in terms of colour, physique, behaviour, etc. is due to single nucleotide polymorphism

(SNP) which constitutes just 0.1%. Importance of such individual variations in health and disease is an important basic principle of ayurveda and was underlined by Charaka some time 4000 years ago as follows: 'Every individual is different from another and hence should be considered as a different entity. As many variations are there in the Universe, all are seen in Human being'⁵⁶. Ayugenomics⁵⁷ describes the basis of individual variation and it has clear similarities with the pharmacogenomics that is expected to become the basis of designer medicine⁴. Understanding the possible relationship between Prakruti and genome will be important. Functionally, this will involve creation of three organized databases that are capable of intelligently communicating with each other to give a customized prescription. These are human constitution (genotype), disease constitution (phenotype) and drug constitution. Nearly 5800 clinical signs and symptoms are available in ayurvedic texts. Effects of season, time and environmental conditions according to ayurvedic chronobiology principles need to be considered to advice lifestyle modifications followed by dietary advice. More than 1200 species of plants, nearly 100 minerals and over 100 animal products comprise the ayurvedic pharmacopoeia⁵⁸. Thousands of single, multiple combinations and processed formulations are described in ayurvedic literature along with details of drug actions. The extent of this database is large and it can be best managed with the help of suitable computer and software.

Ayurveda: a new discovery engine

Combining the strengths of the knowledge base of traditional systems such as ayurveda with the dramatic power of combinatorial sciences and HTS will help in the generation of structure–activity libraries. Ayurvedic knowledge and experiential database can provide new functional leads to reduce time, money and toxicity – the three main hurdles in drug development. These records are particularly valuable, since effectively these medicines have been tested for thousands of years on people¹. Efforts are underway to establish pharmacoepidemiological evidence-base regarding safety and practice of ayurvedic medi-

nes. Development of standardized herbal formulations is underway as an initiative of the Council for Scientific and Industrial Research (CSIR) New Millennium Indian Technology Leadership Initiative (NMITLI). Randomized controlled clinical trials for rheumatoid and osteoarthritis, hepatoprotectives, hypolipemic agents, asthma, Parkinson's disease and many other disorders have reasonably established clinical efficacy. A review of some exemplary evidence-based researches and approaches has now resulted in wider acceptance of ayurvedic medicines^{41,60}. Thus the ayurvedic knowledge database allows drug researchers to start from a well-tested and safe botanical material. With ayurveda, the normal drug discovery course of 'laboratories to clinics' actually becomes from 'clinics to laboratories' – a true reverse pharmacology approach⁶¹. In this process safety remains the most important starting point and efficacy becomes a matter of validation. Globally, there is a positive trend towards holistic health, integrative sciences, systems biology approaches in drug discovery and therapeutics that has remained one of the unique features of ayurveda⁶³. A golden triangle⁶⁴ consisting of ayurveda, modern medicine and science will converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies. It will be in the interest of pharmaceutical companies, researchers and ultimately the global community to respect the traditions and build on their knowledge and experiential wisdom⁶⁵.



Golden triangle approach proposed in the Chitrakoot Declaration⁶⁴.

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