Chapter 1

GENERAL INTRODUCTION

Natural products have provided us, and continue to provide, essential materials for shelter, for furniture, for food, for clothing, for writing, for colouring materials, for weapons, for gifts, and for the treatment of numerous diseases (Balick and Cox, 1996). Plants have formed the basis of sophisticated traditional medicine systems that have been in existence for thousands of years and continue to provide mankind with new remedies. The first records on the use of natural products for medicine written on clay tablets in Cuneiform are from Mesopotamia and date back to about 2600 BC; among the substances that were used were oils of Cedrus species (Cedar) and Cupressus sempervirens (Cypress), Glycyrrhiza glabra (Licorice), Commiphora species (Myrrh) and Papaver somniferum (Poppy juice), all of which are still in use today for the treatment of ailments ranging from coughs and colds to parasitic infections and inflammation. Egyptian medicines report the use of Bishop’s weeds (Ammi majus) to treat vitiligo, a skin condition characterized by a loss of pigments. More recently, a drug (β-methoxy psoralen) has been produced from this plant to treat psoriasis and other skin disorders, as well as T-cell lymphoma (Gurib, 2006).

The interest in Nature as a source of potential chemotherapeutic agents continues. Natural products and their derivatives comprise more than 50% of all the drugs in clinical use in the world. During the last 40 years, at least a dozen potent drugs have been derived from flowering plants including
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_Dioscorea_ spp.—derived diosgenin from which all anovulatory contraceptive agents have been derived; reserpine and other anti-hypertensive and tranquilizing alkaloids from _Rauwolfia_ species; pilocarpine to treat glaucoma and dry mouth, derived from a group of South American trees (_Pilocarpus_ spp.) in the Citrus family and two powerful anti-cancer agents from _Catharanthus roseus_, the Rosy Periwinkle (Gurib, 2006).

The countless anonymous authors who compiled the treatises of the Chinese, Ayurvedic and other systems of traditional medicine, the untold scribes and the knowledgeable shamans which passed on their locally valued information in a more personal manner, should also be gratefully acknowledged (Balick and Cox, 1996). The vast majority of people on this planet still rely on their traditional _Materia medica_ (medicinal plants and other materials) for their everyday health care needs. It is also a fact that one quarter of all medical prescriptions are formulations based on substances derived from plants or plant derived synthetic analogs; according to the WHO, 80% of the world’s population primarily those of developing countries rely on plant-derived medicines for their healthcare (Balick and Cox, 1996).

It is likely that the profound knowledge of herbal remedies in traditional cultures were developed through trial and error over many centuries, and subsequently the most important cures were carefully passed on verbally from one generation to another. Modern allopathic medicine has its roots in ancient medicine, and it is likely that many important new remedies will be discovered and commercialized in the future, as it has been till now, by following the leads provided by traditional knowledge and experience. European traditions are particularly well known and have had a strong influence on modern pharmacognosy in the West. Likewise almost all
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Societies have well-established customs, some of which have hardly been studied at all. The study of these traditions will not only provide an insight into how the field has developed but it would also be a fascinating example of our possible ability to develop a diversity of cultural practices (Gurib, 2006).

People who use traditional remedies may not understand the scientific rationale behind their medicines, but they know from personal experience that some medicinal plants can be highly effective if used at therapeutic doses. Since we have a better understanding today of how the body functions, we are thus in a better position to understand the healing powers of plants and their potential as multi-functional chemical entities for treating complicated health conditions. Medicinal plants typically contain mixtures of different chemical compounds that may act individually, additively or in synergy to improve health. A single plant may, for example, contain bitter substances that stimulate digestion, anti-inflammatory compounds that reduce swellings and pain, phenolic compounds that can act as an antioxidant and venotonics, anti-bacterial and anti-fungal tannins that act as natural antibiotics, diuretic substances that enhance the elimination of waste products and toxins and alkaloids that enhance mood and give a sense of well-being (Gurib, 2006).

Modern allopathic system usually aims to develop a patentable single compound or a ‘magic bullet’ to treat specific conditions. Traditional medicine often aims to restore balance by using chemically complex plants, or by mixing together several different plants in order to maximize a synergistic effect or to improve the likelihood of an interaction with a relevant molecular target. In most societies today, allopathic and traditional systems of medicine occur side by side in a complimentary way. The former treats serious acute conditions while the
latter is used for chronic illnesses, to reduce symptoms and improve the quality of life in a cost-effective way (Gurib, 2006).

A fairly high percentage of useful plant derived drugs were discovered as a result of the scientific follow-up of well known plants used in traditional medicine, and it can be presumed that this is a good approach for discovering other useful drugs from plants. In contrast, other approaches, such as massive biological screening of randomly collected plants, and their phytochemical examination with the aim of identifying new chemical compounds have often not proved very helpful in discovering new drugs. Farnsworth et al. (1985) has rightly inferred that of about 119 plant derived pure drugs used worldwide, 88(74%) were discovered as a result of the phytochemical studies conducted to isolate the active substances responsible for their use in traditional medicine. Among the majority of developing countries, the cost of importing drugs on a large scale is almost prohibitive. On the other hand, these countries have an enormous wealth of information on medicinal plants, which are not only cheap and abundant but also culturally acceptable. Furthermore, most developing countries have neither a well organised pharmaceutical company nor the manufacturing capacity to isolate large quantities of active principles from plants, should they be discovered (Fransworth et al., 1985).

Thus, programmes for drug development in these countries have to be well planned and coordinated. Such programmes should focus on the initial need to produce safe and effective galencial products and in the long term attain the objective of discovering the active principle. These programmes could eventually lead to the development of a pharmaceutical industry in the country.
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Critics of the use of galencial products rather than pure active compounds should consider the case of *Atropa belladonna* as an example. A chemically standardised tincture of *Atropa belladonna* for use in treating stomach ulcers has a therapeutic efficiency at least equivalent to that of a standard dose of atropine sulphate which is the major active principle of *A. belladonna* (Fransworth et al., 1985). The plant can be cultivated in any country and the manufacture of a stable standardised tincture will require little in the way of hard currency, which would be needed to import tablets of atropine sulphate. Even if the active principles have not yet been identified in some of the plants used in traditional medicine, historical evidence of the value of such plants could result in useful preparations, provided they are safe (Fransworth et al., 1985).

There are four basic ways in which plants that are used by tribal peoples are valuable for modern medicine:

1) Plants from the tropics are sometimes used as sources of direct therapeutic agents. The alkaloid D-tubocurarine extracted from the South American jungle liana *Chondrodendron tomentosum* is widely used as a muscle relaxant in surgery. Chemists are still unable to produce this drug synthetically in a form that has all the attributes of the natural product and therefore collection from the wild is still relied upon. Surprisingly harvesting of medicinal plants is often less costly than artificial drug synthesis. Another good example to illustrate this feature is Reserpine, an important hypotensive agent extracted from *Rauwolfia*. The synthesis of this molecule would cost three times as much as opposed to collection (Gurib, 2006).
2) Tropical plants are also used as starting points for the elaboration of semi-synthetic compounds. An example of this would be saponin extracts that are chemically altered to produce sapogenins necessary for the manufacture of steroidal drugs. Until recently, 95% of all steroids were obtained from extracts of neo-tropical yams of the genus *Dioscorea* (Gurib, 2006).

3) Flora from the tropics can serve as sources of substances that can be used as models for new synthetic compounds. Cocaine from Coca plants, *Erythroxylon coca*, has served as model for the synthesis of a number of local anesthetics such as procaine (Gurib, 2006). New and unusual chemical substances found in plants will continue to serve as blueprints for novel synthetic substances and will prove to be increasingly important in the future.

4) Plants can also be used as taxonomic markers for the discovery of new compounds. From a phytochemical standpoint, the Plant Kingdom has been investigated in a haphazard manner; some families have been relatively well studied while others have been almost completely overlooked. For example, many uses have been documented for the Liliaceae and the family is known to be rich in alkaloids. Little, on the other hand is known on the Orchidaceae. Some plants from the family have been investigated because of their close relationship to the Liliaceae. Research has shown that they are not only rich in alkaloids but that some of the alkaloids are unique and could prove useful in the future (Gurib, 2006).
Human health cannot be considered in isolation, for it depends highly on the quality of the environment in which people live: for people to be healthy, they need healthy environments. Health risks are no longer merely a result of localized exposures to "traditional" forms of pollution – although these still certainly exist. They are also a result of broader pressures on ecosystems, from depletion and degradation of freshwater resources, to the impacts of global climate change on natural disasters and agricultural production. Like more traditional risks, the harmful effects of the degradation of ecosystem services are being borne disproportionately by the poor. However, unlike these more traditional hazards, the potential for unpleasant surprises, such as emergence and spread of new infectious diseases, is much greater (Alves and Rosa, 2007).

Biodiversity depletion diminishes the supply of raw materials for drug discovery and biotechnology, causes the loss of medical models, affects the spread of human diseases, and also threatens food production and water quality (Chivian, 2005). Its reduction has direct effects on the discovery of potential medicines. The story of taxol and the Pacific yew illustrates how we may be losing new medicines even before species have been analysed for their chemical content. The commercially useless Pacific yew was routinely discarded as a trash tree during logging of old growth forests in the Pacific Northwest region of the United States until it was found to contain the compound taxol, a substance that kills cancer cells by a mechanism unlike that of other known chemotherapeutic agents: it prevents cell division by inhibiting the disassembly of the mitotic spindle (Cowden and Paterson, 1997). The discovery of the complex molecule taxol and its novel mechanism of action have led to the synthesis of several taxol-like compounds that are
even more effective than the natural compound. This illustrates how a clue from nature can lead to the discovery of a new class of drugs that would have been extremely difficult to discover in the laboratory.

The other example that deserves mention is the peptide compounds in the venom of cone snails, a genus of predatory snails numbering about 500 species that inhabit tropical coral reefs. The diversity of these compounds is so great that it may rival that of alkaloids in higher plants and secondary metabolites in microorganisms (Olivera et al., 1990). Some of these peptide compounds, which have been shown to block a wide variety of ion channels, receptors and pumps in neuromuscular systems, have such selectivity that they have become important tools in neurophysiological research and may become invaluable to clinical medicine. One voltage-sensitive calcium-channel blocker, omega conotoxin, binds with enormous specificity to neuronal calcium channels and has been found to have potent activity in animals both as an analgesic and as a means of keeping nerve cells alive, following ischemia (Olivera et al., 1990).

One critically important service ecosystems play in controlling the emergence and spread of infectious diseases is by maintaining equilibria among predators and prey, and among hosts, vectors and parasites in plants, animals and humans. Wild populations of numerous species are overexploited around the globe, the demand created by the traditional medicine being one of the causes of the overexploitation. In this context, research opportunities should focus both on the documentation of the traditional uses of animal and plants in Traditional Medicine (TM) and the cultural and ecological aspects associated with such practices (Alves and Rosa, 2005). It is quite clear that the practice of TM is not immune to the current
environmental crisis facing our planet. Significant changes in forests, savannas and other vegetational types have impacted on the procurement and preparation, as well as the cost of plant medicine. Desecration of spiritual spots, sacred spaces, and grooves has tended to reduce the dignity of such 'landscapes' and to encourage their abuse (Anyinam, 1995).

Under the impact of industrialization and urbanization, Western medicine has displaced indigenous medical systems in many areas, in the process leaving many indigenous groups of people without any health care. Also Traditional medicinal knowledge is rapidly disappearing, owing to cultural changes and the declining access in both urban and rural areas to sources of natural medicinal products. Most villages in the world are no longer surrounded by the natural habitat that formerly served as a medicine cupboard, and bodies of folk knowledge that have accumulated and been owned for thousands of years are disappearing at an alarming rate. The procurement of plant and animal species needed by indigenous medical practitioners currently requires long distance travel. This affects not only operational costs of providing traditional medical services particularly in urban areas, but also the forms of herbal medicines prepared. For example, freshly prepared herbal medicines are increasingly being replaced by different concoctions, tinctures and powdered forms even in rural areas in order that they can be stored for longer periods without losing their potency or getting spoiled.

Despite the importance of TM for public health in many parts of the world, the practitioners of ethno medicine (especially herbalists and cult healers) appear to be at a greater risk of extinction than even forests and other biomes. Knowledge of the use of plants is disappearing faster than the plants
themselves. The destruction of tropical forests has meant, in many parts of the tropical region, increasing disappearance of native peoples who have been living in these areas and who have accumulated a compendium of folk knowledge about the usefulness of plants for curing various diseases.

The value of biodiversity to human health has been amply highlighted in literature (Grifo and Rosenthal, 1997), one of its most obvious benefits being the large proportion of the pharmaceutical armamentarium it derived from the natural world. Over 50% of commercially available drugs are based on bioactive compounds extracted (or patterned) from nonhuman species, including some lifesaving medicines such as cytarabine, derived from a Caribbean sponge, which is reputed as the single most effective agent for inducing remission in acute myelocytic leukemia. A great number of these natural products have come to us from the scientific study of remedies traditionally employed by various cultures, most of them being plant derived. It is widely accepted that folk or traditional medicinal uses (ethno medical information) of plants indicate the presence of biologically active constituents in a plant. In other words, folk or traditional medicinal uses represent 'leads' that could be a shortcut to the discovery of modern medicines.

Traditionally, the commoditization of plant medicine and animal parts was an insignificant aspect of the practice in TM. In the last few decades, however, there has been a marked increase in the sale of herbal remedies, precipitating large-scale harvesting of medicinal plants, factory-like production of herbal drugs, and animal poaching in many parts of developing countries. Most medicinal plants are gathered from the wild, and countries like India and China reportedly harvest 90 per cent and 80 per cent of their medicinal plants respectively from uncultivated sources (Correa, 2002).
Around 200 medicinal plant species have been added to the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES) appendices (Ten and Laird, 1999) due to such overexploitation.

The interdependence between the sustainability of the environment and the sustainability of the human species needs full recognition and the development of new public health practices, which can increasingly translate into policies and actions that recognise the sustainable use of finite natural resources and will be major determinant for health in future.

It is well established that TM plays a crucial role in health care for a large part of the population living in developing countries. In fact, for centuries, TM was the only health care system available for the prevention and treatment of diseases in different cultures. The interfaces among public health, TM and biodiversity conservation encompass a number of relevant and contemporary issues which are becoming increasingly apparent, as exemplified by WHO's goal in medicines: "to help save lives and improve health by ensuring the quality, efficacy, safety and rational use of medicines, including traditional medicines, and by promoting equitable and sustainable access to essential medicines, particularly for the poor and disadvantaged". Moreover, there is a growing recognition that knowledge of TM is important not only because of its potential to discover new treatments, but also because of its socioeconomic, conservationist and cultural components.

As a concluding note, it would be apt to cite a perspective rightly pointed out by Bodeker and Kronenberg (2002): public health researchers must lead the development of a research agenda that considers social,
cultural, political and economic contexts, to maximize the potential contribution of TM to healthcare systems globally.

Introductory notes specific to the different aspects of this study are given at the beginning of the respective chapters. Hence they are not mentioned here to avoid repetition.