Discovering Our Gifts from Nature Now and in the Future.

Part II

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Abstract: Traditional medicine, the use of plants, animals, and minerals for human health needs must be brought to a new scientific level of sustainable development in order to accommodate future global health care needs.

Key Words: Traditional medicine; safety; efficacy; standardization; intellectual property rights; sustainable development

"Man and nature are indissolubly joined"
Ralph Waldo Emerson, Nature, *1836*

INTRODUCTION

The past century was one of unprecedented scientific and technical advances, coupled with a concomitant explosive expression of artistic fervor. This was accompanied by numerous sociological transformations, dramatic improvements in living conditions, and vast enhancements in human rights. They were also tumultuous times; of world wars, genocides, and totalitarian ideologues. The population grew profoundly, and placed unprecedented demands on the environment of Earth, particularly on its non-renewable, fossil-based resources. Entire natural systems established over millennia were eradicated or seriously eroded. Gradually, as the century progressed, the calls which had begun in the 19th century were heard, and environmental concerns came face to face, in a frequently confrontational manner, with diverse cultural demands for the basics of life, wherever that life was being expressed. Transitioning into a new millennium, the follies of the past are now more deeply understood. This paper will examine the impact of this past century on how most of the people in the world heal, namely, through the use of traditional medicines, and what the implications of these global changes might be for the future of global health care.

In the previous paper[1], I began an examination of the derivation of currently used medicinal agents from higher and lower plants. It was mentioned how these agents are providing significant therapeutic benefits all over the world; in many instances being "the drug of choice". That paper also discussed how many people in the world, particularly those in the "north", had lost contact with the natural origin of their medicines. We touched on the literature that dates back thousands of years on the use of medicinal plants. We discussed how the drug discovery process currently operates in pharmaceutical industry, and how medicinal plants, and indeed plants in general, currently have a very limited place in that discovery process. In most of the major companies, plants, and even plant-derived compounds play no part whatsoever in how new health beneficent agents are discovered and brought to market.

While these conclusions and inferences may be astonishing to some, they reflect what others feel is only one aspect of a global separation of care. It is clearly the case that the major pharmaceutical companies have a very different agenda for health care than responding to that which the majority of the people of the world actually need on a day to day basis. Thus, one can look at the major killer diseases of the world (Table 1) and ask, "Where is the research into the

Table 1. The Major Killer Diseases of the World

AIDS:	3.1 million deaths per year, 5.5 million new cases
• *Tuberculosis:*	2 million deaths, 8 million new cases
• *Diarrheal Diseases:*	1.9 million deaths, 2.7 billion new cases
• *Malaria:*	1 million deaths, 300-500 million new cases
• *Hepatitis B Virus:*	1 million deaths, 10-30 million new cases
• *SARS:*	to 06/03, 7,761 cases, 623 deaths
• *Tobacco-related deaths:*	3.5 million
Data from the website of the Centers for Disease Control, Atlanta, December, 2003.	

treatment of these dire diseases being conducted?" Which companies are working on new anti-malarial agents, for example? Or one can ask what new drugs have been approved for marketing in the past twenty years in any of these drug categories? Through conducting such an examination it will become apparent that these are not diseases that apparently warrant much of the $21.6 billion devoted annually by American pharmaceutical companies to research and development of drugs.

Yet, it is well-established, that at some level of health care, provisions are being made, using local resources, on a daily basis, for the "treatment" of these disease states, as well as many other, non-life threatening diseases, all over the world. That is the role of what is referred to as traditional medicine.

During the past ten years there has been a dramatic increase in the use of phytotherapeutical products in many developed countries. In the United States, for example, approximately $4.12 billion of such dietary supplements were sold in 2000[2]. In some European countries, there are explicit and cogent regulations which govern the labeling, content, and use of phytotherapeutical entities. In the rest of the world there exists a very interesting and dramatic parallel between the medicinal uses of plant materials in the developed and the developing worlds: NEITHER GROUP OF PRODUCTS IS REGULATED.

From a consumer perspective, two aspects of this situation are particularly troubling. The first is that it is very much the era of "Buyer Beware" in both instances. Whether you are going to your local health food store or to your local shaman, hakim, or curandero, you are "buying blind". Whether you go to a local market in Peru and buy a medicinal plant preparation, or whether you buy a fancy package of capsules described as containing a certain amount of golden seal in a health food store in Chicago, you, the consumer, have no idea what you are *really* buying. I fervently believe that a continuation of this situation, on a global basis, substantially undermines the credibility of natural product research and of the role that it should be assuming in health care now and in the future. We need to re-vision this role to regain the scientific, moral, and societal stature of our science.

This dangerous and unacceptable situation has arisen in developed countries because of the widespread belief in two myths. The first myth is that natural products are safe, particularly if they have been used for hundreds of years in a system of traditional medicine. There are several false assumptions underpinning this myth; one of which is that the "safe" plants can be distinguished from similar toxic plants. Another is that the dose of known toxic plants, such as aconite, can be modulated to a safe, effective level without scientific input.

The second common myth is that consumers think that the contents of a box or a bottle of a dietary supplement which contains plant, or fungal, or marine products are somehow regulated. This arises, in part, because of the placement of rows of dietary supplements across the store aisle from OTC products, which are regulated. Do we as natural product scientists wish to perpetuate this situation? Or do we have a different vision? Indeed, isn't it essential to have a different vision?

Before examining various aspects of traditional medicine now and in the future, it is important to make a strong connection with Earth once again, and to recognize the fragile, very thin shell of biosphere which supports the unique diversity of life on this planet. We must also be aware of the unintended impact that widely used chemicals may have on the environment. The banning of DDT in many countries after bird populations declined is now legendary. Now there is the disastrous situation with one of the great predatory birds of the world. The white-backed vulture, *Gyps bengalensis*, was once the most common bird of prey in Asia, now it is threatened with extinction. After years of declining populations, the reason has recently become apparent: the dead birds all had gout, a buildup of uric acid as a result of kidney failure. How did they suddenly all have kidney failure at the same time? Apparently, because their primary food source, dead livestock carcasses, was contaminated with diclofenac, a compound widely used in India and Pakistan in veterinary medicine for a variety of ailments[3].

In a recent book, E.O. Wilson, one of the great naturalists of the world today, has said "Humanity is the species forced, by its basic nature to make moral choices and seek fulfillment in a changing world by any means it can devise."[4a] In other words, at any point in time, we, *Homo sapiens*, are the only species on the planet which has the creativity (and destructiveness) to evoke a situation in which the choice of perpetuation or extinction of a diversity of life on our plant is ours. Such choices may be made in government offices, in corporate board rooms, in the offices of environmental groups, or in legislative councils, but they will be made. And

as a result, *Homo sapiens* will either perish or survive. Those decisions will be intrinsically involved with our environment, for its survival is inextricably interwoven with ours. Wilson says that "....in wilderness is the preservation of the world."[4a] And that without those resources, our lives, and those of all the other species on the planet, are under threat. Thus he calls for an urgent, global land (and water) ethic for remediation, investigation, and conservation which will be based on the best that science and technology can provide. Are we prepared for this challenge?

About 25 years ago, James Lovelock put forward a new version of a concept that indigenous peoples have recognized intuitively. Lovelock called the concept Gaia, Mother Earth, and he proposed that we see Earth as a whole, integrated, living organism[5]. An organism in which there is the continuous interdependence, interaction, and recycling of all biological material, including humans. He spoke of the global effects of a single perturbation to the overall delicate balance, and of the need to see ourselves as just another part of the organism in transition. It is this interweaving of all of the elements of Gaia, including humankind, that we have yet to truly grasp. We are not separate from the other millions of organisms on Earth, but we do have responsibilities towards all of the other organisms. Without them, we cannot survive.

As initiatives proliferate for the manned and unmanned exploration of nearby and distant moons and planets, the Earth and its richness still beckon. In truth, we have only just begun to explore the range of species on Earth. Between the Bacteria, the Archaea, and the Eukarya, about 1.5 to 1.8 million species have been described and named. However, estimates of the true number of species on Earth ranges from 3.6 million to as many as 100 million[4b]. It is one of the principal challenges to humanity to discover the diversity of these gifts from the Earth, and to elucidate, through the optimum use of science and technology, how they can be utilized and delighted in by all humankind[4c].

New species of organism in almost every phylum are continuously being discovered. One extreme (and amazing!) example is that the most abundant organisms on Earth, the *Proclorococcus*, a genus in the picoplankton, were not discovered until 1988. Within the multicellular organisms, the smallest, the fungi, have about 69,000 named species, although 1.6 million are thought to exist[4d]. There are probably many flowering plants still to be identified. About 275,000 species have been described, and each year about 2,000 species are added to the *Index Kewensis*. Even in areas of the world which are well studied, such as North America, new species are regularly being discovered[4e]. At the higher level of the amphibians, the number of species increased from 4003 to 5282 between 1985 to 2001. Some areas of the world remain poorly studied, and once such area has been the Annamite Mountains which lie between Vietnam and Laos. Recently, four new, large mammal species were identified in this remote area. One of these, discovered in 1992, is a 200-pound, oryx-like animal called a saola (*Pseudoryx nghetinhensis*). It is one of the rarest mammals on Earth and how many exist in the wild remains unknown[4f]. In spite of the dearth of even such basic knowledge as to the diversity of life on the planet, calls for the urgent and complete mapping of all biological diversity go unheeded[4d].

And where is this biological diversity predominantly located? It is estimated that over half of the plant and animal species of the world occur in the tropical rain forests. In one part of the Manu National Park over 1300 species of butterfly were identified. And from a 10 hectare area in the Peruvian Amazon 365 species of ants were identified[4g]. Biological diversity represents the extreme of chemical diversity, and thus the higher potential for biological activity.

Of all of the millions of species that inhabit planet Earth, there is only one that has irrevocably impacted all of the other species in such a powerful and deleterious manner, *Homo sapiens*. Have we forgotten what "sapiens" means? There is only one species that has the potential to act to save what remains for all of the generations of the millions of species for the future. That species is also *Homo sapiens*. There is an essential, absolutely core aspect that all humans must consider in order to avoid the utter destruction of this planet. What will allow us to make the transition to an interplay of global cultures which renders the biosphere sustainable for the foreseeable future? Fresh water and arable land are already at dangerously low levels in many parts of the world, even at current population levels. What happens when the population expands to 10-11 billion by 2050? It has been estimated that for every person in the world to reach the present levels of non-renewable consumption in the United States with the current technologies would necessitate FOUR more planet Earths![4h] Already, Earth has lost its ability to regenerate, unless there are dramatic shifts in global consumption and global production from renewable resources.

Population changes have a dramatic impact on the continuing future viability of an inhabitable Earth. In this regard, there is good news and bad. Worldwide, the average number of children per woman fell from 4.3 in 1960 to 2.6 in 2000[4i]. (This figure, 2.1 children per woman, balances birth and death rates. However, improvements in health care, resulting in longer life expectancy, would enhance the population.) Eventually though, the population of Earth will peak. The question is when, at what level, and as a result of what? War? Famine? Disease? Natural disaster? Even if fertility continues to fall at the current rate, the population will still reach 10.7 billion by 2050. In the developed world, for example, in northern Europe, population growth rates are declining substantially. Thus, population control in the developing world is undoubtedly the fateful key for the future of the resources of the planet as the relentless drive towards a higher-level of consumption continues.

The composition of the daily diet plays an important factor in the ability of the available arable land to support a given population. If everybody ate the way that the average American family eats, the 1.4 billion hectares currently used for crop farming and animal husbandry could support only 2.5 billion people. If there was a shift to a vegetarian diet, then the same amount of land could support 10 billion people[4j].

The most profound form of habitat destruction is the clearing of the forests[4k]. In the past fifty years, no other single activity has had such a devastating and irreversible effect on biodiversity. Globally, 45 percent of the tropical rainforest and 60 percent of the temperate hardwood forest has been lost. Although they comprise only 6 percent of the land, the tropical rainforests contain about half of the known species on the planet. Peru has the second highest level of tropical rain forest remaining (as of 1990), and the lowest annual deforestation rate of the countries in northern South America[4l]. Peru is also home to one of the world's twenty-five "hot-spots", the tropical Andes, where the species are most at risk of extinction. If deforestation and other forms of environmental destruction continue at the present rate, at least one fifth of all species will be extinct or threatened with extinction by 2030[4m]. This number increases to one-half by the end of the century. Already, in our insatiable desire to enhance civilization, we have wreaked havoc on biodiversity. Our challenge is not to make that an unforgivable legacy which prohibits the survival of a sustainable population.

Earth remains our home. In the short term, we think and act locally. We innately struggle to think in broader, longer terms with a different set of values. Yet, that is what we must all do in order to establish a global environmental ethic, for our sons and daughters, and their sons and daughters, before it is too late. Others are concerned with respect to energy, plastics, construction, and food from renewable resources. Our focus here is health care, specifically drugs, and, more succinctly, traditional medicines, and what must occur in that area of science to have quality, science-based, sustainable health care system of medicinal agents to which all people in the world have access.

The role of traditional medicine

It was estimated many years ago that over 80% of the worlds' population in developing countries used plant materials as their source of primary health care[6]. This number is even higher today as populations in the developing world have continued to expand steadily in the past twenty years, and drug costs have escalated.

The classical view of what constitutes a regulated drug in the United States, and much of the developed world, is a single chemical entity which, in its purest form, has been rigorously evaluated for its biological, pharmacological, toxicological, and clinical effects[7]. When the product is synthetic and has stereogenic centers, then the focus is also on chiral purity of the biologically active form[8,9]. Substantial chemical efforts in terms of efficient synthesis of an optimized structure, and exhaustive testing of increasingly potent analogues, are behind each new drug entity introduced. A novel, biologically active natural product soon fits into this development protocol.

As discussed in the first paper[1], bioactivity-directed fractionation is the process whereby the compound responsible for a given activity in a natural product extract is isolated and characterized[10]. Modification of the compound, through strategic functional group manipulation, occurs as it proceeds through the various stages of the development process, with a view to enhancing potency, reducing toxicity, or modifying solubility. If the active area within the molecule, the pharmacophore, can be identified, synthetic chemistry around this unit may be initiated in order to achieve the same purposes[11]. Only in relatively rare instances, does the isolated natural product itself serve as a

"magic bullet" which can be approved as a marketable chemical entity. In Paper III in this series we will examine in more detail how this knowledge may play a part in the exploration of potential drugs for development.

An alternative natural product preparation, frequently derived from a traditional medicinal plant, is the multicomponent compound mixture. Such a preparation, which may be comprised of several closely related, biologically active compounds (e.g. gingko flavonoids, capsaicinoids, valepotriates), is marketed when the separation of the individual chemical entities is very difficult, or not-cost effective, and/or is not required by regulation. Mixtures of this type are usually characterized chemically or biologically, although one expectation is that standardization will, in the future, involve both chemistry and biology.

Another type of natural product preparation is that derived from a single plant. Sometimes, this is the pulverized plant part (roots, leaves, fruits, etc) which is then encapsulated, tableted, or prepared as a tea or a poultice. Alternatively, the preparation may be a lyophilized aqueous or alcoholic extract which has been dried and powdered. Expressed oils and essential oils would also be included in this category. These preparations are comprised of very complex mixtures of compounds, and standardization chemically, (other than a "fingerprint" HPLC or gas chromatographic profile) is impossible, although cursory analysis is often important for the purposes of authentication[12]. Biological standardization is essential in these cases, but is almost never accomplished. Also marketed in some parts of the world, particularly derived from the Chinese system of traditional medicine, are preparations which contain multiple plant extracts, since the view is to look at both cause and symptoms for a disease state from a holisitic point of view. Again, biological standardization is essential. At the local level, fresh plant material is often regarded as being crucial for the preparation of teas, etc. in order to optimize effectiveness[13]. These medicines, and those which can be found as single plant preparations in the local markets all over the world, are classified as traditional medicines. One of the greatest challenges for the natural product sciences is at the interface between these preparations and health care. The challenge is to establish those which are safe, those which are efficacious, and those which can be made available in a sustainable manner. The remainder of this article will focus on these precepts.

Knowledge regarding traditional medicines

Traditional medicine is a component part of complementary and alternative medicine, a term which refers to the diversity of non-Western medical practices from various cultures which are now practiced. Ethnomedicine is very broadly defined as the use of plants by humans as medicinal agents[14,15] and is a discipline within ethnobotany[13]. In many areas of the world, the terms ethnomedicine and traditional medicine are synonymous, they differ though from the perspective of commerce. There is a sense that the codification of the use of plants for ethnomedical purposes, and the subsequent marketing of those plants and incorporation into a wider medical practice, establishes those plants as part of a system of traditional medicine.

There are many widely recognized systems of traditional medicine which have evolved and are practiced today; they include the Chinese system, and the Ayurvedic, Unani, and Kampo systems. For the most part, these are well documented systems, and have been so for hundreds, or in some cases, thousands, of years. At a quite different level of familiarity and general knowledge is that information which might be collectively referred to as herbalism. These systems tend to be very localized, maybe even to the individual healer, they are rarely documented, and they are typically passed on through an apprentice system. Scientific evaluation of this knowledge is therefore made more challenging, as there are frequently difficulties even with establishing the nature of the plant(s) used and the method of preparation of the medicine.

The diverse information regarding the use of plants as medicinal agents may, therefore, come from a variety of sources. There are the old Chinese, Middle Eastern and Indian texts, and the various herbals prepared and used widely in Europe in the Middle Ages. There are numerous texts on various traditional medicine systems which have been published in English or in the respective native languages. There are numerous review articles and published surveys of local practices, often organized by disease state. There is on-going field-work, and there are hundreds of years worth of plant specimens collected and catalogued in the herbaria of the world which are annotated with commentary regarding ethnomedical uses. Stunningly, there is no single place in the world where an effort is being made to acquire and correlate this plethora of intensely valuable information for future generations. Two partial, albeit extensive, database

systems do exist, and efforts to maintain and enhance them continue. One of these is the NAPRALERT database at the University of Illinois at Chicago[16,17], and the other is operated at the United States Department of Agriculture by Dr. James Duke[18].

The NAPRALERT (Natural Products Alert) database was founded in 1975 under the leadership of Professor Norman Farnsworth at the University of Illinois at Chicago, acquiring information on the ethnomedical uses, biological (*in vitro, in vivo,* and in human) evaluation and chemical constituents of plants. It is a relational database and thus can be used to provide prioritized lists of plants for study, based on the correlation and comparison of ethnomedical, biological, and clinical information. Presently (February, 2004), it contains information on 46,766 species of higher plant. Of these, 14,301 species have ethnomedical data associated with them, and they represent 3,701 genera and 272 plant families. For 5,705 (39.9%) of these ethnomedically used plants, no compound has been isolated.

If there are about 275,000 species of higher plant recognized as being on Earth, then at least 17% have been used ethnomedically. And have these books and records of reported medicinal use proved of value in drug discovery? One example is that of Gerard's *Herball.* This master work first published in 1597 is still being published today. In almost 1400 pages, it provides detailed discussions of the uses of medicinal plants, investigation of which has so far yielded 16 currently prescribed drugs, including aspirin and digoxin[19]. It is one example of the treasure trove of documented information which may well be a crucial lifeline to the identification of affordable and sustainable medicinal agents in the future.

Making traditional medicines safe

There is a continuing notion among many users of traditional medicines that they are safe for human consumption. Part of this assumption is based on extensive prior experience that may have been gathered over thousands of years. It is thought that this accumulated experience has eliminated from ethnomedical use, those plants which consistently proved toxic or variably effective. However, because of the complexity of the preparations that are being interwoven, and the concomitant use of over-the-counter and prescription products, the use of traditional medicines is in need of a substantially more carefully considered botanical, chemical, and biological scientific approach. Some progress is being made in this direction, but the needed effort is much greater. An outlined framework for these studies is offered at the conclusion of this paper.

The World Health Organization has begun to publish a series of monographs on selected medicinal plants[20]. Volume 1 contains 28 monographs and Volume 2 includes 30 monographs. Volume 3, which is presently being adopted and finalized contains 31 monographs. These are not pharmacopoeial monographs, but are comprehensive scientific references. Each monograph follows a standard format: a pharmacopoeial summary for quality assurance, and a section on the medicinal uses, pharmacology, safety issues, and dosage forms, followed by references. There are no implied endorsements for efficacy or use.

In the United States, the American Herbal Pharmacopoeia and Therapeutic Compendium is also publishing a series of monographs[21]. Thus far, six were published each in Series 1, 2, and 3, with a further seven proposed for Series 4. The monographs focus on those phytotherapeuticals which are most popular in the U.S. market. More recently, the AHP has announced that it will provide botanical and chemical reference materials to interested parties to aid in quality control[22]. While these efforts are certainly appropriate, they are only an interim step on a pathway which must place the health beneficent interests of the patient first, as a result of excellent science on the marketed product.

Consumer Issues

As in any consideration of health care, and as clearly stated in the Oath of Hippocrates, which physicians typically subscribe to, the most important facet of health care is to do no harm. This becomes a fundamental tenet of the examination of traditional medicines. From the viewpoint of the consumer, it is necessary to consider what are some of the minimal consumer expectations that should be in place globally for traditional medicines? What is it that consumers should be demanding from science for their traditional medicines and phytotherapeutical agents?

The past ten years have witnessed a very dramatic increase in the number of phytotherapeutical products from various traditional medicine systems around the world which are

entering the commercial markets in developed and developing countries. Although the very varied regulatory requirements being applied to these products in various countries are of great concern, generally, the quality of the science (botany, pharmacognosy, chemistry, and biology) being conducted on them is steadily increasing. However, because of the absence of clear and harmonious regulations regarding quality control and marketing, the issues of safety and efficacy are being both understated and neglected. The need for a substantially expanded scientific base for the American botanical supplement industry has been indicated, and a number of specific areas where investigation was critically needed have been described[23]. The WHO has issued a set of general guidelines for the study of traditional medicines in the form of a handbook[24]. The stated aims are to harmonize the terms being used, summarize the issues for developing research methodologies, improve the quality and value of research in traditional medicine, and provide appropriate evaluation methods to facilitate the development of regulation and registration of traditional medicines.

In the developed world, and also in many developing countries, phytotherapeutical products are frequently taken with other medicinal agents, both over-the-counter (OTC) and prescription. When these latter products were originally approved by regulatory agencies, there was no consideration of the concomitant use of herbal products. Now, the issue of the clinical interactions of prescription and over-the-counter products with phytotherapeutical agents and traditional medicines has become a very serious clinical issue. It is an issue which requires substantial scientific study and development from the perspective of public awareness and safety. There are numerous reports of these herb-drug interactions[25]. One of the common ones is that of St. John's Wort (SJW) and a broad range of drugs including indinavir, cyclosporin, digoxin, fluoxetine, clozapine, warfarin, and theophylline[26]. This is because a diverse array of constituents in the extracts of SJW are biologically active and can induce certain drug-metabolizing enzymes in the cytochrome P450 system, and possibly can alter serotonin concentrations[27]. Another example is that of the platelet activation inhibitors (gingko, grape seed, etc) which may cause complications of excessive bleeding during surgery.

One of the most important inferences from the burgeoning sales of phytotherapeutical products is that the scientific literature associated with them is expanding correspondingly. Consequently, continuous evaluation of the literature relating to analytical procedures, to biological and chemical information, and to clinical trials on phytotherapeutic and traditional medicinal agents everywhere in the world, becomes a very important aspect of safety.

There are some limited concerted attempts underway to establish the active principles of several of the major phytotherapeutical and traditional medicine products; for two prime reasons. The first is to establish the nature of the active principle for the purpose of using that compound analytically to determine the likely effectiveness of successive batches of the plant-based medicinal agent. Such an approach is not adequate if there is any possibility that a separate, potentially toxic, principle is also present in the plant sample. The second purpose, and one that will be looked at more carefully in Paper III in the series, is that of drug discovery; the search for new molecules derived from a traditional medicine which have the potential to be developed as drugs.

Currently, in the United States and elsewhere, substantial compromises with respect to consumer safety and product effectiveness are being made. One of these compromises is the use of a single marker compound to characterize a plant extract chemically. These constituents may or may not be the active principle, but are frequently used to characterize extracts or plant materials giving an often false impression of standardization, somehow equating that with safety and or efficacy. Unfortunately, a plethora of other major issues regarding phytotherapeutical products and traditional medicines are presently being largely ignored, or their potential effects mollified, in the United States. Yet, typically, consumers are unaware of this lack of assurance with respect to safety and efficacy.

An overall program for developing more comprehensive standards for the safety and efficacy of these plant-based products is needed in most countries in the world. The first aspect to be assured is that the correct genus and species of plant material is being offered, and that the correct plant part is being used. Different plant parts of the same plant contain very different constituents, and thus to substitute a root part for a leaf, or a fruit for a twig, could result in toxicity rather than effectiveness. Consumers should be assured that the plant material or preparation is free of contaminants such as insects, (illegal) pesticides, solvent residues, heavy metals, aflatoxins and other toxic fungal metabolites, and radioactivity. Countries from which some plants are imported have different pesticide standards and may be using illegal

pesticides, herbicides, and even plant growth hormones to improve crop production.

Adulteration, the deliberate addition of biologically active materials to a plant preparation, has become a significant issue in the United States and elsewhere in the past few years. Several products have been withdrawn as a result of the demonstration of the presence of added ingredients to phytotherapeutical preparations. One example is the product PC-SPES, a multicomponent extract of mostly Chinese herbs, which had found widespread (and quite successful) use in lowering prostate specific antigen levels in men following prostate cancer surgery. Batches of the product were found to be adulterated with a variety of synthetic drugs[28] and the United States Food and Drug Administration ordered the product withdrawn from sale. A recent report by Ernst[29] has focused on the adulteration of Chinese medicinal herbal products with synthetic drugs. Some of the synthetic agents detected include: aminopyrine, indomethacin, phenylbutazone, and various corticosteroids.

There is a need for chemical and biological reproducibility and stability on a batch to batch basis. Thus, it will be necessary to have integrated chemical and biological systems developed which can correlate the stability of the active principle(s) with biological activity over time, and thereby establish a meaningful shelf-life. As the active principles become known, the authentication of primary reference standards will need to be improved substantially. In addition, there will be a need to develop quick, cheap, accurate, and clinically relevant biological systems for the demonstration of biological activity for each batch of marketable product. The actual content of dietary supplements versus claimed content from a label has been an issue for many years. We have shown that of 21 samples of capsicum cream, less than half (43%) met the labeled content[30]. Five of the products had no capsaicin, only a synthetic substitute. Analysis of twenty commercial ephedra products showed that 11 of them either failed to indicate other alkaloids being present, or had a greater than 20% variance between batches[31].

Extraction techniques may change over time as the need to optimize the active principle(s) in the preparation becomes apparent and as solvent costs or alternative isolation techniques, such as supercritical fluid systems, are introduced. This will mean that safety issues regarding the new extract will need to be re-established, and thus monographs for specific drug preparations and their standardization will need to be developed and continuously updated as scientific standards evolve. Efforts to enhance the bioavailability of herbal preparations will be more forthcoming through liposome preparations and other forms of controlled release formulation. At each of these changes and improvements, it will be necessary to re-establish the stability of the preparation chemically and biologically, as well as the shelf-life of the product in order to assure consumers that the product is likely to be efficacious on repeated purchases.

Sustainability, with respect to both the use of solvents for primary extraction, as well as in the cultivation of the plant material, will become important future criteria. Already we have seen that once a traditional medicine (e.g. ginseng) or a phytotherapeutical product (e.g. golden seal) becomes a major marketed entity, then wildcrafting of the plant (taking a plant from only wild sources such as the forests or the meadows) can almost eliminate that plant, if agricultural techniques for crop development are not introduced. Shinwari and Gilani studied a small community in Astore, in northern Pakistan[32]. Thirty-three plant materials were being used. One plant, *Betula utilis*, had almost been driven to extinction (because it lived up to its' species name too well!). Two plants were recommended for rapid *in vitro* development, and another was suggested for a sustainable harvesting program. The need for education of the local populace regarding conservation and development of medicinal resources was emphasized.

The deleterious effects of wildcrafting can also be seen in the oceans. Just fifty years ago, the oceanic whitetip shark was regarded as the most common in the world. Less than 1% of that population remains in the Gulf of Mexico today, due to fishing (and unintentional trapping) for other species (tuna and swordfish), for food (sharkfin soup), and for medicinal agents (shark cartilage)[33]. WHO has issued a set of guidelines for good agricultural and collection practices (GACP) for medicinal plants[34]. The guidelines are specifically aimed at the protection of medicinal plants, and the promotion of their cultivation, collection, and use in a sustainable manner which conserves the medicinal plant and the environment.

In spite of these efforts, overall, the present scientific and regulatory situation regarding the marketed phytotherapeutical and traditional medicinal agents is no longer acceptable from a public health perspective in either

the developed or the developing countries. A more concerted effort by major international bodies, legislative groups, professional organizations, and industrial consortia is urgently needed to harmonize the regulations applying to the status and quality of these preparations which are, and will remain, the core of the global health care system.

Protection of indigenous rights and appropriate compensation

In the past twelve years, the area of intellectual property rights has become the most contentious and difficult area of natural products chemistry and biology. It is a vast topic, and opinions on its significance and implementation vary widely. In the years before the Convention on Biological Diversity, many scientific groups and organizations, both formally and informally, recognized that countries and individual groups had the right to take control of their biological property, both marine and terrestrial[35]. In addition, there was a recognition that the knowledge gained by indigenous groups which formed the basis of their ethnobotanical and ethnomedical practices could be protected[36,37].

The implementation of the Convention on Biological Diversity codified a myriad of these intellectual property issues. It also instructed sovereign nations to develop plans to catalog and preserve their indigenous knowledge and their biodiversity[37,38]. With respect to the issues of accessibility, it proposed that Contracting Parties "endeavor to create conditions to facilitate access to genetic resources for environmentally sound uses..." In response to this suggestion, some countries chose to impose strict regulations and an overarching bureaucracy to control access to their biome[39]. Other countries chose to strongly encourage interested parties to work with local personnel and try to develop relationships at the scientific level which could foster development without exploitation. Our experience at UIC, which is probably typical, is that we have worked diligently, and at substantial expense, with a number of countries and local groups in the past ten years to develop agreements for access to biome in exchange for different forms of compensatory packages depending on local conditions and requests[40]. Unfortunately, we have now chosen not to continue to collect plant samples in certain countries, either because of their unacceptable and restrictive policies, or because the penalties, in the event of not meeting requirements were so onerous as to be very seriously restrictive of our academic rights. As I have stated elsewhere[41] "the Earth Summit...may, in the long term, be one of the most profound steps ever taken in natural products chemistry". For there to be a long term positive impact, there must greater understanding, flexibility, and consistency in procedures, or the outcomes for all parties may not necessarily be positive.

The impact of the CBD on the scientific and clinical study of traditional medicine is very profound. Protecting and compensating local groups for their indigenous knowledge, and for providing access to the biome, is a reasonable expectation for both those who hold the resources and those who are seeking them[36]. Compensation may take any one of a number of forms, and we have been involved in many of these initiatives, including developing training programs for individual personnel on-site and at UIC, developing laboratories through the provision of equipment, and providing symposium programs[40]. Longer term forms of compensation may include sharing in any royalties or productivity payments and offering first right of refusal for indigenous crop development[36]. For field work, American universities require the investigator to develop, and have approved, an interview protocol for the questions to be asked of traditional healers and patients. These protocols also typically require relationships to be established with local personnel for the conduct of surveys acquiring such knowledge. Thus, it is essential that academic institutions, both in the United States and in the country whose traditional medicine is being studied, have effective technology transfer groups to negotiate these relationships[42].

These protections and considerations for the source of the knowledge and for compensation, including the timeframe and the nature of the compensation, are required because of the potentially significant commercial aspects of the knowledge and its development. A native plant cannot be patented. However, a particular extract of a plant, with a defined biological use can. There are several recent examples where this has occurred; even in instances where the knowledge was previously well-documented. As an individual molecular entity, a natural product can not be patented. Patenting the compound, new or old, must be tied to a non-obvious biological activity. That activity is usually initially in a cell- or enzyme-based system, and is then followed up with activity in an appropriate animal model. Frequently, closely related compounds are prepared and evaluated in order to establish, in a preliminary manner,

aspects of the structure activity relationships. For licensing purposes, the acquiring company typically wishes for a substantial level of exclusivity when such an asset is acquired. Thus, a higher value for a patent is placed on a compound with structural novelty and with some derivatives produced which offer information regarding structure activity relationships. An even higher premium is evident if the compound is novel, there is some SAR established, and the biological mechanism of action is unique.

The drugs from traditional medicine

As mentioned in the previous paper[1], when serious investigations began of plant materials for their constituents in the early part of the 19th century, the first materials examined were some of the most popular plants used medicinally at that time, for which activity had been demonstrated. Thus, in a period of a very few years, morphine, quinine, cocaine, atropine, caffeine, and emetine were all isolated in various degrees of purity. As chemistry and biology developed, so more of these materials used in traditional medicine were examined and some of them became drugs. Fabricant and Farnsworth[43] have recently updated the information in this area. They showed that only 94 species of plant are utilized for the production of these drugs, and that of the 122 single agent natural products that are used as drugs around the world, 72% were used for the same or a related ethnomedical purposes. Thus, with about 275,000 species of plant on Earth and at least 46,766 of them with reported medicinal uses, there should be abundant resources available for the discovery of new medicinal agents for the future. In the next paper we will address the question of how this can be achieved.

Since organic chemistry began to be employed for the structure determination of natural products, there has been a concomitant effort to examine both the chemical and biological changes that could be wrought on a given structure. This is the foundation of the science of medicinal chemistry. Two aspects of this approach will be mentioned here because they are relevant to the development of agents derived from traditional medicine. The first is that direct elaboration of a natural product template derived from a traditional medicine may lead to compounds which are possibly more active and less toxic than the original compound. Secondly, if, through synthesis and structure modification, the structural unit within the molecule responsible for the biological activity can be determined, the so-called pharmacophore, selective elaboration of this unit may also yield compounds which have enhanced potential to be drugs. Two examples will illustrate these points.
The first is the development of verapamil, a drug used for hypertension and overcoming drug resistance, from the smooth muscle relaxant drug papaverine (Figure 1). The second is that of galegine, which is derived from *Galega officinalis*, used ethnomedically for the treatment of diabetes. Based on this structure, metformin, the first of the biguanidine antidiabetic drugs, was developed[43]. There are many other examples.

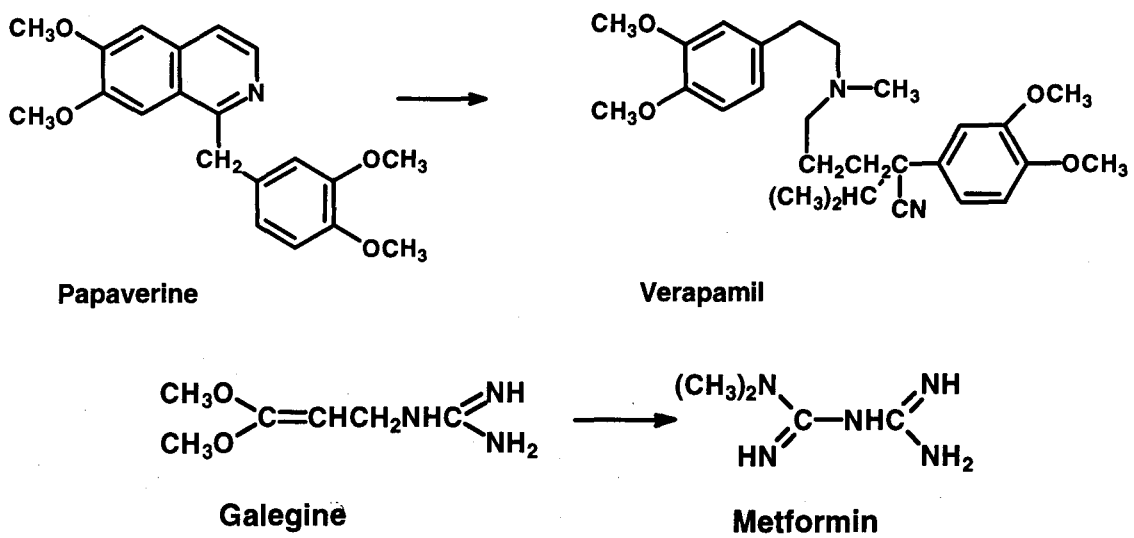
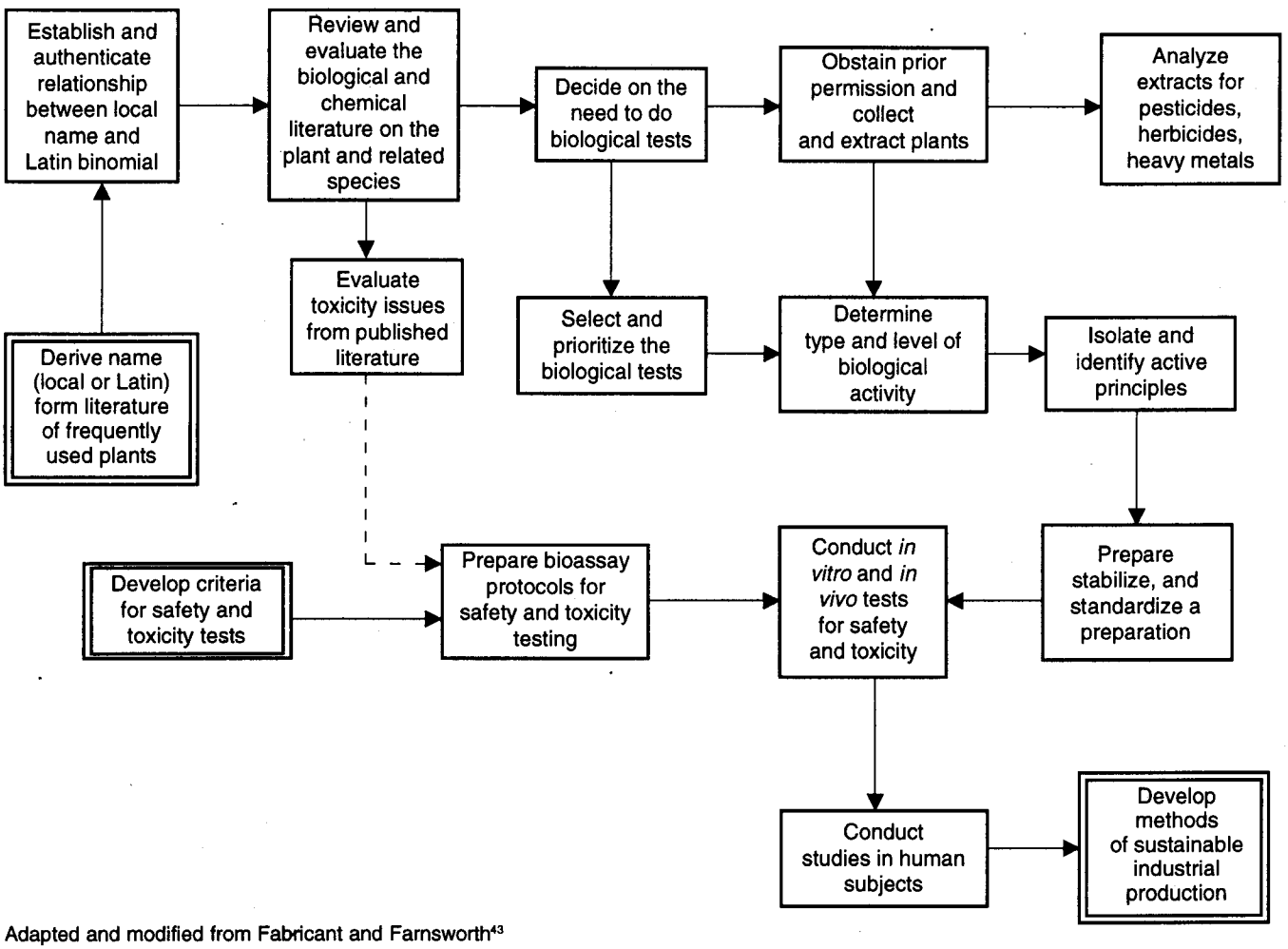


Figure 1. Natural products and their elaborated pharmacophores (adapted from Fabricant and Farnsworth)[43].

Standardization of Traditional Medicines

We can now begin to develop a strategy for the study of traditional medicinal plants which is focused on a safe, standardized preparation. This approach was first considered by Farnsworth and colleagues in 1985[6], and subsequently by Fabricant and Farnsworth[43], and is expanded on here (Figure 2).



Adapted and modified from Fabricant and Farnsworth[43]

Figure 2. A Flow Chart for the Study of Plants Used in Traditional Medicine

If one begins with a previously documented or reported plant, the first consideration is to check for the correct spelling of the local name and see whether there are any known synonyms. Sometimes, the same local name is given to several plants which may appear to be the same plant, or which are different plants, but which have the same use. The next step is to verify the Latin binomial for the plant and also derive any synonyms for that binomial in the event that the literature may have data reported for the same plant under two (or more) binomial names. Review of the biological and chemical literature is next. This may involve other closely related plant species (the same genus usually) and should include *Chemical Abstracts, Biological Abstracts,* and *Index Medicus.* In addition, as many sources of ethnomedicine information should be consulted as possible, so that a clear picture of whether the plant has been used elsewhere in the world for similar or other purposes can be determined. It must be emphasized that this type of literature work, like any other literature work in science is an on-going process. The data obtained from the literature must now be analyzed for breadth, depth, and appropriateness. What compounds have been isolated? From which plant part? Are any of them

possibly responsible for the observed activity? Has the biological and possibly clinical testing been carried out appropriately, with the necessary controls? Have the biological data been interpreted correctly? Based on this information, which may be very extensive or almost non-existent, decisions will be needed with respect to the highest level of biological tests that can be applied to the chosen extract(s). Another aspect of biological activity which may be available from prior testing data relates to toxicity. Are there any reports of toxic side effects from the plant in question? Are there specific extraction, preparation, or dosage issues to be considered? Are there known toxic metabolites from related species?

Acquisition of the plant material for study may require a number of levels of approval and negotiation depending on the whereabouts of the plant (forest or marketplace) and where and how the various aspects of the work will be conducted. In addition, licenses may be needed to export the plant material or the extracts derived from it to another country. Even if a plant is purchased in a local market, positive identification, some idea of the origin of the plant, and the preservation of a voucher sample with notes (or better a herbarium specimen) are needed. Negotiations to acquire plant material from the field may take some time as legally binding agreements are developed. Only when these formalities are completed, can field work with a local collaborator commence. Preferably, most or all of the scientific work should be done in the country of origin, with only minimal influence from outside laboratories. But in many countries of the world, that is simply not possible. More will be said on this topic in Part III. Analysis of the extracts for pesticides, herbicides, heavy metals, and where considered important, known adulterants is the next step, so that when the biological data is determined in the selected assays, there is a high level of assurance that activity is due solely to the plant constituents. Bioactivity-directed fractionation is an important phase of the process because it may yield the compound, or group of compounds, responsible for the activity, and may demonstrate whether other compounds in the extract interfere with the potentiation of the activity. In other words, fractionation could afford clarification as to how to prepare a standardized preparation. Once there is good information regarding the active principles, investigations can begin as to what might be the nature of the preparation to be tested for potential marketing, which active compounds to use as chemical markers, and which tests to develop for batch-to-batch biological evaluation. Stability testing can start once a standard preparation has been determined and characterized, and this preparation is the one to be used for all *in vitro* and *in vivo* testing, prior to any testing in human subjects. Finally, it may be necessary to enlist crop specialists to develop methods for the sustainable production of the medicinal plant as a crop.

As we consider the enhanced scientific study of traditional medicines from the aspect of the identification of the active agent for standardization purposes, there are other reasons, including drug discovery, and mechanism of action to be considered as justifications for the intense investigation of traditional medicines. There is also the potential for countries to develop enhanced self-reliance and independence, resulting in a decrease in the importation of medicines from the north. Thus, the necessity to develop the scientific foundations for traditional medicine in a given country is also economic. We have seen how the desperate needs for treatments for the major diseases of the world are being poorly served through the research efforts of the major pharmaceutical companies. Seizing the opportunity is therefore critical.

One of the model approaches to this issue which was recently initiated in South Africa, is the in-depth scientific examination of local resources used as traditional medicines for a variety of important diseases. The project is funded by the South African government and is a broad collaboration between a number of different groups representing different areas of botanical, chemical, biological, and pharmacological expertise. The program is aimed at searching for new medicines, and looking for "proof of principle" for traditional medicines.

The costs and environmental concerns relating to the discovery and production of synthetic drugs will continue to rise in the next fifty years. As a result, there will be an ever increasing need for alternative, natural, sustainable sources of medicinal agents, compounds, derivatives, extracts, and teas. Because of the vast knowledge base that is the foundation of traditional medicine, those plants that are used in various traditional medicine systems will become critically important in the provision of primary health care, if the scientific examination of these products can begin before the plants themselves disappear. More discussion of this topic and the whole area of the future development of natural products will be presented in Part III in this series.

SUMMARY

Traditional medicine is frequently viewed by allopathic physicians as crude, misguided, inappropriate, and dangerous; and sometimes it is. Yet over 80% of the population in the developing world relies on the effectiveness of such medicines on a routine basis for their primary health care. As the population grows in the next fifty years, it is essential that they become the core of primary health care in the world based on good science. These traditional medicines require intensive and urgent investigation in the next few years from a botanical, chemical, and biological perspective, particularly for the diseases of the developing world. Marketed products must have received a level of scientific attention to assure safety, efficacy, and consistency for the consumers who rely on them. Validated and standardized traditional medicinal agents must become a critical component in a vision for sustainable global health care.

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