Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Ethnopharmacology xxx (2005) xxx–xxx
Journal of ETHNO-PHARMACOLOGY
www.elsevier.com/locate/jethpharm

Perspective paper

Some thoughts on the future of ethnopharmacology

Geoffrey A. Cordell*, Michael D. Colvard

Department of Oral Medicine and Diagnostic Sciences, College of Dentistry, University of Illinois at Chicago, Chicago IL 60612-7231, USA

Accepted 23 May 2005

Abstract

A discussion is offered of the future potential role of ethnopharmacology in global health care.

Keywords: Ethnopharmacology; Medicinal agents; Traditional medicines; Future strategies

1. Introduction

"The presence of this tiny sheet of paper proves the presence of the whole cosmos". (*Thich Nhat Hanh*, Being Peace)

"...the ability of ecosystems to sustain future generations can no longer be taken for granted". (*Millennium Ecosystem Assessment*, United Nations, April, 2005)

"All nature is at the disposal of humankind. We are to work with it. For without it, we cannot survive". (*Saint Hildegarde of Bingen, 12th Century, quoted in Matthew Fox*, Original Blessing)

"If you are on the fifth step and you think you are too high, you will never make it to the sixth step". (*Ajahn Chah*, A Still Forest Pool)

"With a stout heart, a mouse can lift an elephant". (*Tibetan proverb, quoted in Feldman*, A World Treasury)

Perhaps there is nothing more to be said. Perhaps if we can see the deeper reality in those quotations and aphorisms, and can evolve as visionary global citizens and scientists, all will be well. Perhaps. But to understand the "how", it's all in the details, as Mies van der Rohe indicated (1959).

When you think about the future of ethnopharmacology, the first thing you have to do is to step out of the box. Working in the existing box is not proving to be optimal for us as a group of scientists. Did you know that? Do you feel that? There are some quite fundamental aspects of what we do that have to change, for us and for the community we serve. Let us try to explain, and by the end of the article we hope that you too will feel the need to step out side of that proverbial box. In my view, we must be on a mission, perhaps to try to save health care based on natural resources, no less. As Lao Tzu said, "Each journey starts with a single step" (Lao Tzu, 1990). Let our first step be the topic of oil and how it relates to the future of ethnopharmacology.

"G.M. (General Motors) is...reallocating engineering resources to rush the next generation of large sport utility vehicles...into production by the end of the year. G.M. is also...abandoning some planned small and midsize sporty cars" (Hakim, 2005).

They are doing WHAT?! Oil recently hit record highs of over US$ 60 per barrel (Bloomberg.com, 2005). Estimates are that it will go even higher later this year, and may reach US$ 135 per barrel within 3 years (Sherer, 2005). It is estimated that based on the known, reasonably accessible oil reserves, global production of oil will peak sometime late in 2007 (Campbell, 2002; Anonymous Peak Oil, 2005a). According to the United Nations and other sources (Anonymous, 2005b), and based on current estimates of known reserves, production capacity, and usage, the global oil supply may last another 60–70 years, albeit at steadily escalating costs.

* Corresponding author: Tel.: +1 312 413 5381; fax: +1 312 355 2688.
E-mail address: cordell@uic.edu (G.A. Cordell).

0378-8741/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jep.2005.05.027

No less than 96% of our transportation needs are based on oil (Anonymous, 2005b). Nature gave us this gift of oil only once. What we have now, no-one else on this planet will ever have again. Ever. And yes, it is all there in that piece of paper. All of the myriad connections. Everything. We are living an illusion of no limits.

Since 1987 (Cordell, 1987, 1990, 1993, 1995a, 2000, 2002a,b,c, 2003, 2004), one of us has been writing about the future of pharmacognosy and its' "fit" in the world. Whether the topic of discussion is related to the evolution of pharmacognosy (defined as *"The study of biologically active natural products"*) or ethnopharmacology is moot. The real topic is what health care, particularly the use of medicinal agents for the prevention of disease and for treatment, will look like in 20, 30, and 40 years from now, By this time the global population is estimated to be at least 9.2 billion (United States Census Bureau, 2005a), 44% more than today (United States Census Bureau, 2005b).

So let's pause here for a moment. What do *YOU* envisage health care using medicinal agents to look like in the next 20, or 30, or 40 years? On a global basis, what will those medicinal agents be? Currently, 75% of prescription drugs sold in the United States are synthetic, and many of the remaining 25% are semisynthetic derivatives of natural products (Farnsworth and Morris, 1976). Is that the global model we should be striving for? Remember, it may take 10, 15, 20 years, or even (as in the case of camptothecin) 30 years, to transition a compound from the bench to the market. In *your* vision, what will be the origin of those medicinal agents? Who will be producing them, and where? How will they be regulated? Will those agents be different in the developed compared with the developing world? From where will enough raw material originate for the production of synthetic and semisynthetic drugs for a population of 8 or 9 billion people, and at prices that are affordable?

But here are some confounding factors to consider: (i) population growth will occur mostly in the developing world; populations will actually decline in many European countries and Japan (United States Census Bureau, 2005c); (ii) at the present time it is estimated to cost about US$ 800 million to bring a new single agent drug to market in the US (Di Masi et al., 2003; Adams and Brantner, 2004); (iii) the technology and biotechnology which can be applied to the biological evaluation of plant extracts and compounds is advancing at a breathtaking pace; (iv) there has been vast degradation of the many global ecosystems (United Nations, 2005); and (v) there are new killer diseases emerging (SARS, Marburg virus, avian flu virus, etc.), and drug resistance to the known antimicrobial, antiparasitic, and anticancer agents is on the rise (Anonymous, 2000a). *How does this change your vision?*

And . . . for the ethnomedical reports on about 14,300 species of plant in NAPRALERT (about 5.2% of all plant species), 58% of these species have never been examined biologically or chemically (Cordell and Quinn-Beattie, 2005). Yet, of those plant-derived products currently available as prescription products, 74% are used in a manner which parallels their ethnomedical use (Fabricant and Farnsworth, 2001). *How about your vision now*?

As you know, drug discovery is notoriously inefficient. Depending how you estimate compounds synthesized, only about one in a hundred thousand or more compounds evaluated biologically will make it to the market as a drug (Adams and Brantner, 2004). The major pharmaceutical companies have no, repeat *NO*, interest in screening higher plant (or marine or fungal) extracts for their biological potential. Programs evaluating plant extracts have been closed for several years. Antibiotic drug discovery screening of cultured broths has almost stopped. There are some small biotech companies doing natural product drug discovery, and their hope is to bring potent, novel compounds to the larger pharmaceutical companies for further development. But there is not a single company in the developed world which is basing its discovery strategy on ethnopharmacology. *And NOW what is your vision for health care in 2025 or 2040?*

Several years ago, we began an article on alkaloids and drug discovery with the phrase "We need to talk" (Cordell et al., 2001). Now we need to talk some more. We need to talk critically and strategically amongst ourselves in forums and in groups at scientific meetings. We need to be more proactive in formulating a consolidated view of where ethnopharmacology must "fit" in the scheme of global health care. And then we need to talk in a much larger arena. We need to assemble the "choir" and then we need to sing, *VERY, VERY* loudly, all over the world. We need a new vision for the natural product sciences and ethnopharmacology embracing a strategy based in contemporary and evolving science and technology that is relevant to global future health care needs.

Let us examine some "plausible futures" based on contemporary thinking of those outside of ethnopharmacology. The millennium ecosystem assessment (United Nations, 2005) examined four such future scenarios, all of which require a change from our present deleterious relationship with ecosystems: *Global Orchestration*, *Order from Strength*, *Adapting Mosaic*, and *Technogarden*. These scenarios differ based on whether global development paths are increasingly globalized or increasingly regionalized, and on two different approaches to ecosystem management, based on whether actions to issues are reactive or proactive. Many factors were considered, including population growth, per capita income, land use change, nutrient loading, and climate change. Under each of the examined scenarios the global temperature is expected to increase by 1.5–2.0 °C by 2050. This climate change will result in significant habitat loss, and predominantly negative economic effects throughout the world. It will also lead to possibly 10–15% extinction of plant species. In one of the scenarios, *Order from Strength*, which focuses on reactive policies in a regionalized world, health care in the developing countries could become worse "as economic inequality increases and as commerce and scientific exchanges . . . decrease". The other three models foster more promising health care scenarios.

Two aspects related to ethnopharmacology were examined: biochemicals and genetic resources (p. 182) and infectious disease regulation (p. 187). Several areas, including botanical medicines, cosmetics and natural personal care, and crop protection and biological control were anticipated to increase in intensity. Meanwhile, it was concluded that ecosytem modifications had led to increases in numerous infectious diseases on a global basis, including malaria, meningitis, leishmaniasis, dengue, Japanese encephalitis, African trypanosomiasis, Chagas' disease, schistosomiasis, filariasis, and diarrheal diseases. These effects have occurred and will continue to occur mostly in the tropical areas of the world.

Let's briefly examine some current issues that face the use of plant materials in health care.

2. Current issues in ethnopharmacology

2.1. Traditional medicine knowledge acquisition

At least 80% of the worlds' population in developing countries use plant materials as their source of primary health care (Farnsworth et al., 1985). The knowledge about these systems may be held individually or tribally or documented in well-established tomes. It is not held, or made available anywhere in the world, as the result of a global cumulative effort. Thus detailed scientific analysis of the global data is impossible. NAPRALERT at UIC (as of May, 2005) has information on 14,317 species with ethnomedical data, representing 3703 genera and 272 plant families (Cordell and Quinn-Beattie, 2005). This represents about 5.2% of all estimated higher plant species.

But are these records of reported medicinal use of value in drug discovery? One example is that of Gerard's *Herball*, first published in 1597, which has so far yielded 16 currently prescribed drugs (Cox, 1998). Another is the study of Fabricant and Farnsworth (2001), who showed that 94 species of plant are utilized for the production of the 122 single agent natural products that are used as single agent drugs around the world. Of these, 72% were used clinically for the same or a related ethnomedical purpose. For 8387 (58.6%) of the ethnomedically used plants in NAPRALERT, no compound has been isolated and no biological work conducted (Cordell and Quinn-Beattie, 2005). Thus, even with this very incomplete database of global ethnomedical information, there is abundant opportunity for the discovery of new medicinal agents.

The information that is known and that can be accumulated on the use of plants in health care systems around the world is of inestimable value. It must be sifted, correlated, investigated and potentiated. One aspect of ethnopharmacological information collection that is critical is the accompaniment in the field of a qualified physician (local or external) to provide independent affirmation of the claimed health benefits. We can imagine that the results should focus on either the development of single agent drugs, or one of the other forms of presentation of plant extracts and materials as medicinal agents around the world. Let us examine some of the factors in developing those two tracks in the future.

2.2. Intellectual property rights

For many years, scientific groups and organizations, both formally and informally, have recognized that countries and individual groups have the right to take control of their biological property, both marine and terrestrial (Cordell, 1993), and that the indigenous knowledge at the basis of their ethnobotanical and ethnomedical practices could be protected (Reid et al., 1993; Cragg et al., 1997).

Since the Convention on Biological Diversity (CBD), intellectual property rights regarding access to and acquisition of plants (and all biological organisms), and the indigenous knowledge associated with them, has become a very contentious and difficult area for natural products chemistry and biology. The CBD also instructed sovereign nations to develop plans to catalog and preserve their indigenous knowledge and their biodiversity (Anonymous, 1992; Cragg et al., 1997). Furthermore, it proposed that contracting parties "endeavor to create conditions to facilitate access to genetic resources for environmentally sound use . . ." Some countries chose to impose strict regulations and an overarching bureaucracy to control access to their biome (Anonymous, 1995), while others chose to strongly encourage interested parties to work with local personnel. This is a vast topic, and opinions on its significance and implementation vary widely. The impact of the CBD on the scientific and clinical study of traditional medicines is at the very core of ethnopharmacology and its development as a high impact science in future health care. For one of us (Cordell, 1995a), "the earth Summit . . . may, in the long term, be one of the most profound steps ever taken in natural products chemistry".

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 (Reid et al., 1993; Soejarto et al., 2002). It is essential that academic institutions have effective technology transfer groups to negotiate the relationships between the various academic, corporate, state, and private entities (Thayer, 1992). For there to be a long term positive impact though, there must greater understanding, some flexibility, and yet consistency in procedures, or the outcomes for future health care may not be as beneficial as they could be.

2.3. Traditional medicine safety and standards

The most important facet of all health care is to do no harm (Oath of Maimonides); assuring that whatever is being taken by humans for medicinal purposes is safe. Efficacy is a secondary consideration. Many users of traditional medicines consider that they are safe for human consumption; an assumption based, in part, on extensive prior field expe-

rience. If this notion ever had validity, it is now no longer correct. In many parts of the world, phytotherapeutical products are frequently consumed with over-the-counter (OTC) and prescription products. The clinical interactions of these approved products with phytotherapeutical agents and traditional medicines has become a very serious issue, one which requires careful monitoring and reporting, followed by substantial scientific study and communication to effect public awareness and enhance safety; for the reports of these herb-drug interactions are numerous (Ioannides, 2002).

A very dramatic increase has occurred 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. There are varied regulatory requirements being applied to these products in respective countries (itself a matter of great concern), but as we see from the *JEP* and other journals, the volume and the quality of the science (botany, pharmacognosy, chemistry, and biology) being conducted on them is steadily increasing. An important inference from the burgeoning research on phytotherapeutical products is that the scientific literature associated with them is expanding correspondingly. In 1985, with a much smaller format than currently, *JEP* published 666 pages, and in 2004, 2108 pages. Continuous evaluation of the global literature relating to analytical procedures, to biological and chemical information, and to clinical trials on phytotherapeutic and traditional medicinal agents, consequently becomes a very important aspect of safety and efficacy. Aspects of these concerns are expanded on elsewhere (Cordell, 2003).

What is it that consumers should be demanding from science for their traditional medicines and phytotherapeutical agents? Are we responding to and meeting those needs? Traditional medicinal plants are being marketed all over the world as phytotherapeuticals, but their quality control is typically very poor or non-existent. 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; typically, consumers are unaware of this lack of assurance. The WHO has issued a set of general guidelines for the study of traditional medicines (Anonymous, 2000b). 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 regulation and registration of traditional medicines. In our view, these aims are an important start, but are not adequate for the continuous improvement of plants in health care. Our vision for the future of plants in primary health care must substantially exceed these minimum standards.

An overall program for developing more comprehensive standards for the safety and efficacy of these plant-based products is needed for consumers in most countries in the world. Some details have been discussed elsewhere (Cordell, 2003). An outline is shown in Fig. 1. 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. The plant material or preparation must be free of contaminants such as insects, (illegal) herbicides and pesticides, solvent residues, heavy metals, aflatoxins and other toxic microbial metabolites, and radioactivity. Adulteration of phytotherapeuticals, 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, such as aminopyrine, indomethacin, phenylbutazone, and various corticosteroids.

On a batch-to-batch basis there must be botanical, chemical, and biological standardization of products, and collateral studies which would establish both the safety of the product and a demonstration of its efficacy and meaningful shelf-life. Real time PCR analysis on a microchip will become a standard procedure for the authentication of plant materials (Carles et al., 2001; Zhang et al., 2005). Multi-component analytical systems will have a significant impact in the area of routine chemical standardization. Quick, cheap, accurate, and clinically relevant biological systems, mostly microarray-based, will demonstrate (verify) the level of biological activity for each batch of marketable product (Prasad et al., 2005). There is a very substantial need to collate the incidence, and rationalize the potential, for drug-herb interactions, and to make the patient and the diverse health professions involved fully aware of these risks. As we learn more about the effects of traditional medicinal plants on the human genome through the impact of extensive microarray analysis, both the positive and negative attributes will be clarified. Also, the difference in effectiveness between the pure active compounds and the whole or selected plant extracts will become clearer. Finally, the plant material(s) which comprise a product must be made available on a sustainable basis (Cordell, 2003).

2.4. Sustainability

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 for the success of ethnopharmacology. Once a traditional medicine (e.g. ginseng) or a phytotherapeutical product (e.g. golden seal) becomes a major marketed entity, then wildcrafting (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, 2003). WHO has issued a set of guidelines for good agricultural and collection practices (GACP) for medicinal plants (Anonymous, 2004). 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 both the medicinal plant and the environment.

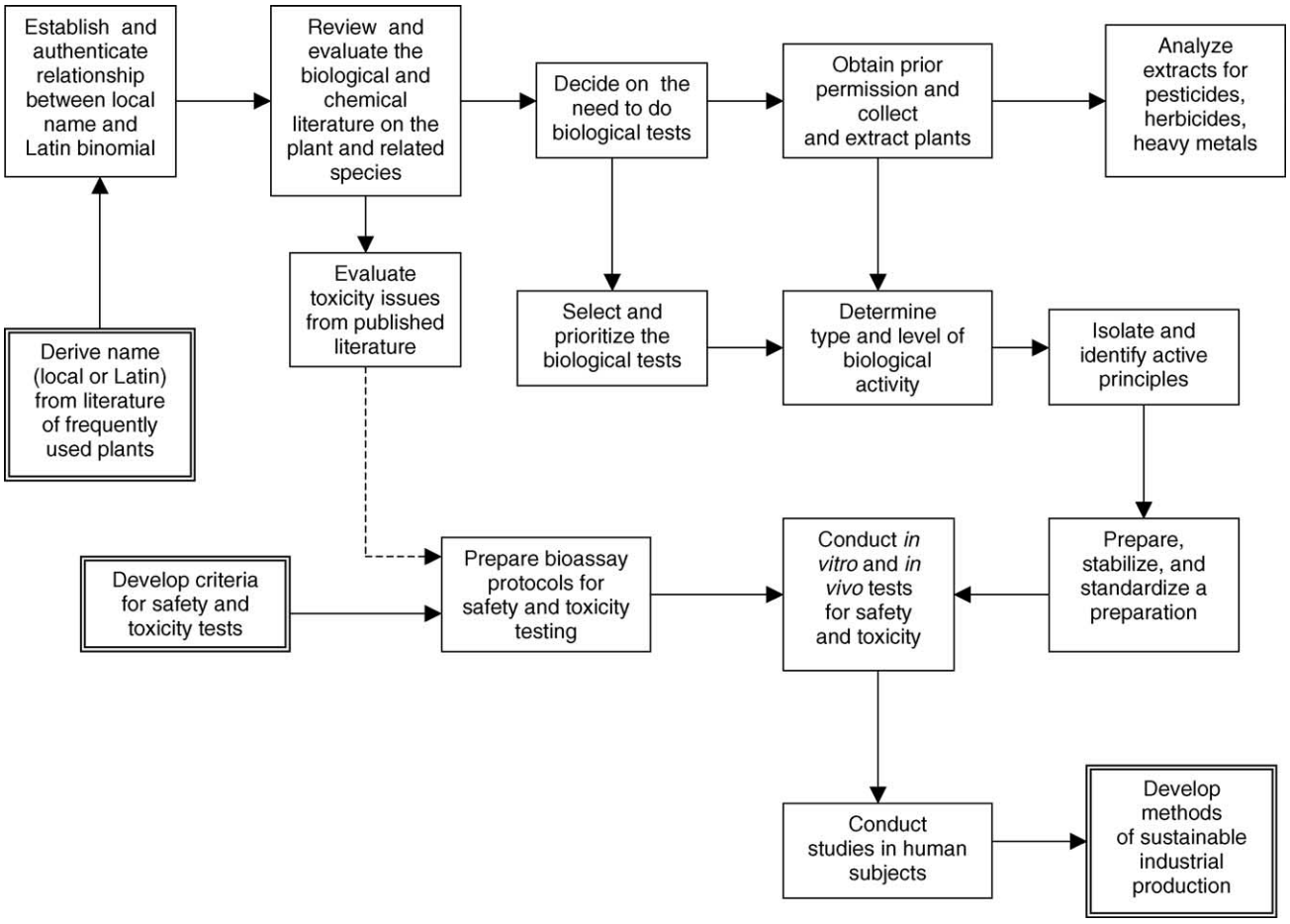

Fig. 1. A flow chart for the study of plants used in traditional medicine.

3. Future of ethnopharmacology

3.1. A vision

For everyone presently on earth to reach the levels of profligacy of the US, four Earths are needed (Cordell, 2002a). Clearly, if humanity is going to survive, let alone continue to evolve, major shifts in the use of renewable versus non-renewable resources are needed. We need a dramatically new vision for the resources we apply to health care, in particular medicinal agents. We can see what the critical issues are for drug therapy (Table 1). What we must strive for is a clearer vision of the ways in which current resources and technologies and those to be developed, can be utilized optimally for the future health care. We need to develop and continually reaffirm a vision that, 30–40 years from now, for some of the reasons outlined above, that there will be a well defined requirement for safe, effective, standardized, and sustainable natural products in global health care. If we do not have the clear vision for our work, then what are we doing? What do we view as our societal role? Which policy makers, strategists and "movers and shakers" are we influencing? How are we measuring that impact?

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 04/04, 8,096 cases, 774 deaths
Tobacco-related: 3.5 million deaths (cancer, lung)

Data from the website of the Centers for Disease Control, Atlanta, October, 2004.

Since 1947, there has been a so-called "Doomsday Clock" ticking . . . how close are we to nuclear disaster? (currently 7 min is the answer). We need to establish a corresponding "chembio clock" . . . how close are we to fully exploiting (using up) the known chemical and biological resources of earth? The millennium ecosystem assessment was probably the closest evaluation yet. So where would we currently be? 15 min to midnight, because of the improvements in crop technology balancing (somewhat) population growth? Or if we measure in terms of known resources and sustainability, 5 min after midnight. In other words, is it already too late? Did that midnight hour pass in 1978 when the global population exceeded the capacity to be sustained by the known resources of Earth? Are replenishment and remediation of ecosystems

a way to "turn back time"? We are not ecologists, and we do not know those answers. But our children and their children need that answer.

Demonstrating value in plants and in marine organisms, for medicinal and health purposes is vital for conserving the remaining biodiversity for future generations. Which countries in the world require an ecological impact assessment, including economic botanical potential appraisals, before rain forest destruction for new commercial development? A "gift" we can make to future generations is to catalogue and collect type specimens, and establish gene banks and libraries of plant extracts for future biological evaluation (Cordell, 1990, 1995b, 2000, 2002a,b, 2004). While there are well-established germ-plasm banks for essential crops, there appear to be no major depositories of the medicinal plants in the world. In the event of a catastrophic disaster, natural or otherwise, this could be a critical omission. Unfortunately, the capacity building efforts which occur through collaboration and the development of the centers of research excellence are not occurring in many countries because of onerous regulatory policies and procedures.

For plants that are used for health purposes, it is our responsibility to propose and initiate the conduct of the diverse investigations on these products, globally and locally. Such broad-based research activities must begin locally, not in a far-flung laboratory in a developed country, and be conducted by local scientists who have the health and welfare of their people and their country at heart. An exploration of this type, for new, biologically significant plants or other natural products will require two fundamental areas of excellence: places and people (Cordell, 2000, 2002b,c, 2004). For success to be achieved in such an endeavor, these two facets must be brought together at the same time as part of a major capacity building effort.

Few countries in the world have a vertically integrated pharmaceutical industry, where a compound or a concentrate can be taken through the complex chemical and biological stages to a finished and approved pharmaceutical entity at the international level. And most of the world uses plant materials (largely in an unregulated and uncontrolled manner) as a primary source of health care. Health ministries should be asking whether there is long-term economic benefit to continuing the importation of refined natural products and synthetic drug compounds. Or is it possible to grow, extract, and standardize any of these materials for local consumption, using local expertise and technology, recognizing the possibility of an export market as the long term goal? Are there local issues which hinder such developments? Is it possible to produce medicinal plants for commerce and have standardization of traditional medicines? Will this strategy meet primary health care needs for most of the world 30 years from now? Is this a conscious improvement in health care for the majority of the world?

For this vision, establishment of local research centers of excellence is needed for the infrastructure (laboratories, offices, and equipment), as well as the trained people to pursue selected areas of the natural product sciences. How will research studies be prioritized in these new centers of excellence? Phytochemical investigations for novel compounds can no longer be supported. How will the newly developed technology be transferred to benefit the local and the global society? The ethnomedically used plants which have yet to reveal active principles, or even be studied, are a significant place to start, but that assumes that all of the pertinent knowledge relating to their use is available. Global and local databases of ethnopharmacologic knowledge in the public domain, including that contained in herbals, are essential, as is their constant updating with new and refined knowledge. A second option of plants for potential investigation are those currently in traditional medical practice whose uses have not been recorded, which raises important intellectual property issues.

Is there a realistic vision for the numerous intellectual property issues related to natural product development? Firstly, there is a profound need for harmonization, within major regions of the world, of the processes and applicable regulations regarding access to the biome. There must be a willingness on both sides, those who have the resources and those who wish to assist in the exploration and potential development of those resources, to initiate and maintain innovative agreements for the training of local personnel, for the establishment of local herbaria and research laboratories, and for the distribution of royalty and licensing income (Soejarto et al., 2002). Secondly, since indigenous knowledge was explicitly included in the CBD, there is a profound need to handle this intellectual property issue, regarding information systems and the correlation of ethnomedical uses of plants in a non-profit, globally available resource. This would allow improved and more rational decision making regarding truly worthwhile research projects and would help to avoid the duplication of research efforts.

3.2. Future impact

It is time now to examine what the future impact of natural products *must* be in global health care as single agent drugs and as standardized traditional medicines.

The approximately 5750 different natural product skeleta, from the perspective of interactions with enzymes and receptors, represent substantially greater chemical diversity space and is more reflective of the chemical diversity space of drugs, compared with the known range of combinatorial compounds (Feher and Schmidt, 2003).

Comparatively, there are relatively few natural products, and of those, very few have been given even cursory biological evaluation (Cordell et al., 2001). As far as the development of single drug agents is concerned, one could make the case for enhanced structure diversification through a number of pathways (Table 2), including combinatorial chemistry, combinatorial biosynthesis, chemistry on plant extracts, find alternative, previously untapped sources (e.g. endophytic fungi, extremophile microbes, or those difficult to culture. There

Table 2
Some strategies to diversify natural product structures

Combinatorial chemistry on strategic natural products
Combinatorial biosynthesis (shifting the gene sequence)
Move the gene sequence to faster growing organisms
Chemistry on plant extracts
Microbial transformation of single or multiple natural products
Potentiating the genes of biosynthesis to realize full metabolic capability
Solid phase stable enzymes for structure modification and synthesis
Plant associated and difficult to grow fungi and bacteria
Use engineered hairy root cultures for valuable natural products
Examine the 80% of plants which have not been tested chemically or biologically

is the future potential of having available the full biosynthetic capacity of an organism, rather than only that present at a particular point in time. Genetically controlling natural product biosynthesis is one of the great challenges at the core of enhancing the consistent availability of biologically significant natural products, either as single agents or as a multiple component mixtures (Cordell, 2004). If plants are to be effective and reproducible "factories" for the production of medicinal agents for a global population, the molecular switches which control the overall pathway, and the specific enzymes involved in secondary metabolite formation, must be profoundly understood (Boonstra et al., 2001). Biocatalysis, using isolated enzyme systems is another approach to enhance natural product structural diversity, and to conduct reactions which have no parallel in organic synthesis (Rathbone et al., 2002).

Less than 20% of all plant species have been evaluated chemically or biologically (Cordell, 2003). And of the approximately 21,200 alkaloids, 76% have never been evaluated in a single bioassay (Cordell et al., 2001). Thus, for single agent drug discovery a natural product library represents a very substantial opportunity in the search for new potent compounds or new mechanisms of action.

It is well-established that drug discovery for a single agent drug is a very inefficient and extremely expensive process. The costs of going from discovery to market and beyond are at least US$ 800 million according to academic (Di Masi et al., 2003) and federal trade commission (Adams and Brantner, 2004) estimates. Of the 5000 compounds which enter advanced pharmacological development only one will become a drug, and this from the prior screening of may be millions of compounds. Even at the phase I clinical trial stage, only one compound in twelve will be marketed (Hileman, 2004; Harding, 2004) and productivity, in terms of FDA approved drugs, is decreasing steadily. For example, whereas 34 new molecular entities were approved as drugs by the US Food and Drug Association in 1999, only 21 were approved in 2003 (United States FDA, 2005). This is extremely wasteful of both human and fiscal resources. As we have seen, the companies are screening millions of samples from their compound libraries, yet there are nowhere near even a million natural products characterized So against these odds what can be our vision for natural products in the area of drug discovery for the future? One of the industry complaints about natural product extracts in drug discovery screening programs is that many plant materials, when recollected, do not confirm the original observed activity. Another significant problem is that many of the active extracts on bioactivity-directed fractionation afford only known active compounds. How can the natural product sciences respond to these challenges?

Assuming that we have available the background information on numerous plants for a particular disease state, there are numerous strategic decisions to be made to discover novel, biologically active compounds (Cordell, 1995a). Collection prioritization, which extracts to test, which biological systems, what constitutes activity, etc. In our many years of experience of operating these programs, there are two critical steps which make the determination of the "intellectual" potential of a plant, and the determination of an active principle inefficient. In a random collection, and a single biological screen, most of the plant extracts tested (often 95% or more) are inactive, and of those that are active, many (sometimes 50%) yield known active principles. Since natural products will only be of interest to pharmaceutical industry if they are novel, potent and operating by novel mechanisms, this is not an effective strategy to developing natural products as single agents or even as traditional medicines, even though the "hit" rate for traditional medicines in a related bioassay is typically substantially higher (20–60%). In addition, many of the isolated active compounds are known. Consequently, we must substantially rethink this aspect of the discovery process in two ways: (i) we must determine the biological significance of a plant in the field, and (ii) we must determine the active principle in an extract directly. We developed a partial approach to this latter issue using a dereplication protocol (Cordell et al., 1997; Cordell and Shin, 1999), involving a HPLC/electrospray mass spectral/bioassay/database system. This process eliminated 50% of cytotoxic extracts from the fractionation process because they would yield a known active.

The in-field biological evaluation of plant materials is significantly more challenging and potentially more rewarding (Cordell, 1995a, 2000, 2004). There is a need to develop simple and robust (in reproducible reporting capability), proteomics-based tests for plant extracts. Then, when activity is observed in an extract obtained on-site, collection of the same plant population can take place. In such a program, only those plants which show activity in a particular bioassay will be collected, dried, and brought to a laboratory for further chemical and biological evaluation. Such studies would also require in-field access to large botanical, chemical, and biological database systems, in real time, to assess prior knowledge regarding the plant in question.

Automation, nanotechnology and proteomics, will have an increasingly important impact on ethnopharmacology, and thus we must be prepared to use them appropriately (Smith, 2001). Microarray assay systems based on the enhanced knowledge of the human genome will be brought to the level of the routine evaluation of extracts and compounds in order

to assess genetic impact. In addition, we will see automated real-time PCR processes such that large numbers of plant samples can be genetically identified at the same time . . . an essential step in enhancing the quality control of medicinal plants.

3.3. Public health agenda

One aspect of ethnopharmacology which is rarely considered is that of the overall impact on public health, and its role in the relationships between allopathic and traditional medicine healthcare systems. Bodeker and Kronenberg have presented a very interesting argument which lays out some of these research issues from a public health perspective (Bodeker and Kronenberg, 2002). Our own set of questions can be formulated based on a vision of two systems functioning in a seamless system of healthcare, rather than the highly fragmented set of practices we see around the world today for most patients.

For example, how can allopathic and traditional medicine practices be more fully integrated into health care systems for the benefit of the patient? In each country, what is the combination of practices which leads to optimal care? How does that occur on the local (individual patient) and the national (health care systems) levels? How will the respective practitioners be integrated into a more effective health care system? What are the economic and health care issues in developing countries for the development of standardized, quality-controlled, effective preparations which can be exported?

Are there real economic benefits to the development of traditional medicine? What is the economic situation considering sustainability, with and without quality controls and the demonstration of safety and efficacy? What is the impact of insurance coverage versus individual patient coverage at point of sale to these questions? What is the nature of the clinical trials that are needed for the demonstration of efficacy of traditional medicines? And from an indigenous knowledge and property protection perspective, will the harmonization of the CBD and the trade related aspects of intellectual property systems (TRIPS) encourage the development of more research on traditional medicines and a higher standard of health care, and provide appropriate compensation to all interested parties?

3.4. An agenda of challenges

In the next 10 years, the internal research programs of the major pharmaceutical companies will become even more focused, and the discovery of new, biologically active entities, whether large or small molecules, will be almost completely outsourced to those with the discovery resources. For single drug entities, discrete molecular entities of high potency and/or unique structure and mechanism will be needed. Regrettably, the drugs developed will not be for diseases/conditions which affect mortality in most of the world (Cordell, 2003). It is the responsibility of the natural product sciences to challenge the *status quo* and effect that change. For ethnopharmacology, We see this as *the* challenge, the development of medicinal agents for the majority of the world. It is one of several ways in which the natural product sciences can, indeed *must*, contribute very substantially to the global health care enterprise.

Table 3
Some challenges for the future of ethnopharmacology

Catalog and preserve the bio- and chemo-diversity of the rainforests and the oceans
Catalog the eco- and ethno-information on plants and their products
Maintain equitable access to the biome and assure intellectual property rights
Develop medicinal plant germplasm banks
Develop integrated global information systems on the uses of medicinal plants
Develop medicinal plants in a sustainable manner
Enhance natural product drug discovery technology in the areas of automation, proteomics, and bioassay targets
Evaluate the known natural products in diverse bioassays
Develop proteomics-based, in-field bioassays
Potentiate the chemical diversity of natural products
Produce vaccines and drugs in fast growing secondary sites
Assure the safety and efficacy of traditional medicines
Develop integrated global alliances for medicinal plant product development
Develop the facilities, the infrastructure and the personnel to conduct the above programs

Some of the critical challenges which lie ahead for the future of ethnopharmacology have been presented, and a selection of these is summarized in Table 3. However, there is a missing component: how will this vision and these goals be achieved? An essential aspect of the vision, one which forms the core for future ethnopharmacology development, is that countries will have an infrastructure that will allow them to develop their own sustainable medicinal agents from natural sources. The goal will be to develop programs to assist countries to potentiate their resources, their facilities, and their scientists in order to evaluate and standardize natural product-based medicinal agents on a sustainable basis for their health care systems.

Our vision is that there will evolve in the years ahead a global alliance for natural product development. Such an alliance will be composed of international agencies (WHO, UNIDO, UNDP, NATO, EU, etc), government agencies (NIH, NSF, NIE, SRC, DAAD, etc), pharmaceutical companies, academic institutions, non-government organizations (WWF, WRI, CYTED, TRAMIL, IFS, TWAS, etc.), scientific societies (IUPAC, RSC, ASP, PSE, GA, JSPS, etc.), and major international foundations (Ford, Gates, MacArthur, Rockefeller, etc.). Globally, to establish such a vast program could cost US$ 10 billion a year, perhaps more. But that is less than half what US pharmaceutical companies spend each year on research and development. It would be the central, yet highly diversified, component in the development of natural product based medicinal agents for health care in the future. We firmly believe that organizing and funding such an ambi-

tious initiative for addressing the challenges cited in Table 2 is absolutely fundamental for the health care for the majority of the people in the world for 20 and 40 years from now.

4. Conclusions

"In wilderness is the preservation of the world" *Henry David Thoreau*

The thin ecosystem which protects and supports the survival of all species on earth is the largely unappreciated miracle in all of our lives. That we continue to destroy this "gift" before we can fully savor it and learn its uses, is the ultimate, unforgivable folly. It was Ralph Waldo Emerson who offered an important reminder about stewardship of the earth: "we did not inherit the earth from our forefathers, we are borrowing it from our descendants". What is the legacy for earth that we are leaving our descendants? Is it one which represents our folly, or is it one of thoughtful, enlightened caretaking? We must continually evolve the vision of the role of ethnopharmacology and the natural product sciences for the future, when the pressures on available resources, including land use, water and oil, will be quite different. We must fully integrate all of the available technologies into developing the societal role of ethnopharmacology in global health care. It is up to us to create these visions, and maintain them for the creative growth of the health care of individuals and for the security and stability of societies. The future of ethnopharmacology *requires* that you be a visionary global scientist.

We must reconnect with the deep obligation that we have to the food supply and to the health care of those future generations. We must create innovative strategies employing all of the associated sciences and technologies in order that the natural product sciences, including ethnopharmacology, can assist in the development, in a sustainable manner, of the foods and the health care products, including drugs, for a dramatically expanding global population. Finally, we must foster the development of multidisciplinary, international, collaborative research programs which will support the local and global scientific development of our natural resources which are essential for the future health of the Earth (Cordell, 2000, 2002c, 2004).

And those quotations at the head of this article? Yes, we must work *with* nature. Yes, we are only on the first or second step; we can go much higher. Yes, we must be mice with stout hearts and lift the elephant, the *status quo*. And yes, whether it is a piece of paper, a bell, or a medicinal agent in the marketplace, the interplay of the whole world is right there. All we have to do to understand our mission is to truly see that.

Finally, a visionary question to ponder, if you could think of something radical that would change the face of ethnopharmacology in its various forms in the next ten years or so, what would that be, and how would you begin to develop and implement it?

Acknowledgement

The author thanks Ms. Mary Lou Quinn-Beattie, University of Illinois at Chicago, for the provision of important ethnomedical data from NAPRALERT.

References

Adams, C., Brantner, V.V., 2004. Estimating the costs of new drug development: is it really US$ 802m? Social Science Research Network December, available at http://ssrn.com/abstract=640563.

Anonymous, 1992. User's guide to global biodiversity strategy. WRI/IUCN/UNEP 3, 1–197.

Anonymous, 1995. Executive Order No. 247 of the Government of the Republic of the Philippines. Issued 18, may, pp. 15, available at www.psdn.org.ph/chmbio/eo247.html.

Anonymous, 2000a. Drug resistance threatens to reverse medical progress. World Health Organization, Geneva, Switzerland, available at www.who.int/inf-pr-2000/en/pr2000-42.html.

Anonymous, 2000b. WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization, Geneva, Switzerland, pp. 74.

Anonymous, 2004. WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants. World Health Organization, Geneva, Switzerland, pp. 133.

Anonymous, 2005a. Peak Oil. The peak in oil production will change everything. May, available at www.peakoil.org.

Anonymous, 2005b. The future of oil. Institute for the Analysis of Global Security, Washington, DC, available at www.iags.org/futureofoil.html.

Bloomberg.com, 2005. Oil falls to 6-week low after IEA cuts global demand forecast. April 13, available at www.bloomberg.com/apps/news.

Bodeker, G., Kronenberg, F., 2002. A public health agenda for complementary, alternative and traditional medicine. American Journal of Public Health 92, 1582–1591.

Boonstra, B., Rathbone, D.A., Bruce, N.C., 2001. Engineering novel biocatalytic routes for production of semisynthetic opiate drugs. Biomolecular Engineering 18, 41–47.

Campbell, C.J. 2002. Forecasting global oil supply 2000–2050. Hubbert Center Newsletter, July, 1–8.

Carles, M., Lee, T., Moganti, S., Lenigk, R., Tsim, K.W.K., Ip, N.Y., Hsing, I.-M., Sucher, N.J., 2001. Chips and Qi: microcomponent-based analysis in traditional Chinese medicine. Journal of Analytical Chemistry 371, 190–194.

Cordell, G.A., 1987. Pharmacognosy: far from dead. American Druggist. March, pp. 96–98.

Cordell, G.A., 1990. Pharmacognosy—the high tech pharmaceutical science. In: Proceedings of the Second International Symposium on Recent Advances in Natural Products Research, Seoul National University, Seoul, Republic of Korea, pp. 24–40.

Cordell, G.A., 1993. Pharmacognosy—new roots for an old science. In: Atta-ur-Rahman, Basha, F.Z. (Eds.), Studies in Natural Products Chemistry. Bioactive Natural Products (Part A), vol. 13. Elsevier Science Publishers, Amsterdam, pp. 629–675.

Cordell, G.A., 1995a. Changing strategies in natural products chemistry. Phytochemistry 40, 1585–1612.

Cordell, G.A., 1995b. Natural products as medicinal and biological agents: potentiating the resources of the rain forest. In: Seidel, P.R., Gottlieb, O.R., Kaplan, M.A.C. (Eds.), Chemistry of the Amazon. American Chemical Society Symposium Series No. 588, Washington, DC, pp. 8–18.

Cordell, G.A., 2000. Biodiversity and drug discovery—a symbiotic relationship. Phytochemistry 55, 463–480.

Cordell, G.A., 2002a. Discovering our gifts from nature, now and in the future. Part I. Revista de Quimica 16, 5–12.
Cordell, G.A., 2002b. Recent developments in the study of biologically active natural products. ACGC Chemical Research Communications 14, 31–63.
Cordell, G.A., 2002c. Natural products in drug discovery—creating a new vision. Phytochemistry Reviews 1, 261–273.
Cordell, G.A., 2003. Discovering our gifts from nature, now and in the future. Part II. Revista de Quimica 17, 3–15.
Cordell, G.A., 2004. Accessing our gifts from nature, now and in the future. Part III. Revista de Quimica 19, 33–41.
Cordell, G.A., Beecher, C.W.W., Kinghorn, A.D., Pezzuto, J.M., Constant, H.L., Fang, L., Seo, E.K., Long, L., Cui, B.L., Barrilos, K.S., 1997. The dereplication of natural products. In: Atta-ur-Rahman (Ed.), Studies in Natural Products Chemistry, vol. 19. Elsevier Science Publishers, Amsterdam, pp. 749–791.
Cordell, G.A., Quinn-Beattie, M.L., 2005. Unpublished results from the NAPRALERT database, University of Illinois at Chicago.
Cordell, G.A., Quinn-Beattie, M.L., Farnsworth, N.R., 2001. The potential of alkaloids in drug discovery. Phytotherapy Research 15, 183–205.
Cordell, G.A., Shin, Y.G., 1999. Finding the needle in the haystack. The dereplication of natural product extracts. Pure and Applied Chemistry 71, 1089–1094.
Cox, P.A., 1998. The promise of Gerard's Herball: new drugs from old books. Endeavor 22, 51–53.
Cragg, G.M., Baker, J.T., Borris, R.P., Carte, B., Cordell, G.A., Soejarto, D.D., Gupta, M.P., Iwu, M.M., Madulid, D.R., Tyler, V.E., 1997. Interactions with source countries. guidelines for members of the American society of pharmacognosy. Journal of Natural Products 60, 654–655.
Di Masi, J.A., Hansen, R.W., Grabowski, H.G., 2003. The price of innovation, new estimates of drug development costs. Journal of Health Economics 22, 151–185.
Fabricant, D.S., Farnsworth, N.R., 2001. The value of plants used in traditional medicine for drug discovery. Environmental Health Perspectives 109 (Suppl. 1), 69–75.
Farnsworth, N.R., Akerele, O., Bingel, A.S., Soejarto, D.D., Guo, Z., 1985. Medicinal Plants in therapy. Bulletin of the World Health Organization 63, 965–981.
Farnsworth, N.R., Morris, R.W., 1976. Higher plants - the sleeping giant of drug development. Journal of Pharmaceutical Sciences 147, 46–52.
Feher, M., Schmidt, J.M., 2003. Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry. Journal of Chemical Information and Computer Sciences 43, 218–227.
Hakim, D., 2005. G.M. to seek cuts in union benefits. New YorkTimes, March 25, pp. C1, C16.
Harding, A., 2004. More compounds failing phase I. The Scientist, August 6.
Hileman, B., 2004. Reining in dietary supplements. Chemical and Engineering News June 21, 21–23.
Ioannides, C., 2002. Pharmacokinetic interactions between herbal remedies and medicinal drugs. Xenobiotica 32, 451–478.
Lao Tzu, 1990. Tao Te Ching. Translation. V.H. Mair. Bantam Books, New York, NY, p. 168.
Mies van der Rohe, L., 1959. On restraint in design. *NY Herald Tribune*, 28 June.
Prasad, R.C., Herzog, B., Boone, B., Sims, L., Waltner-Law, M., 2005. An extract of *Syzygium aromaticum* represses genes encoding hepatic gluconeogenic enzymes. Journal of Ethnopharmacology 96, 295–301.
Rathbone, D.A., Lister, D.L., Bruce, N.C., 2002. Biotransformation of alkaloids. In: Cordell, G.A. (Ed.), The Alkaloids, Chemistry and Biology, vol. 58. Academic Press, San Diego, CA, pp. 1–82.
Reid, W.V., Sittenfeld, A., Laird, S.A., Janzen, D.H., Meyer, C.A., Gollin, M.A., Gámez, R., Juma, C. (Eds.), 1993. Biodiversity Prospecting. World Resources Institute, Baltimore, MD, p. 341.
Sherer, R., 2005. Oil prices pinch other spending. Christian Science Monitor, April 7, available at www.csmonitor.com/2005/0407/p01s01-usec.htm.
Shinwari, S.K., Gilani, S.S., 2003. Sustainable harvest of medicinal plants at Bulashbar Nullah, Astore (Pakistan). Journal of Ethnopharmacology 84, 289–298.
Smith, R.H., 2001. Nanotechnology. Modern Drug Discovery April 32–34 (36), 38.
Soejarto, D.D., Tarzian-Sorenson, J.A., Gyllenhaal, C., Cordell, G.A., Farnsworth, N.R., Kinghorn, A.D., Pezzuto, J.M., 2002. In: Stepp, J.R., Wundham, F.S., Zarger, R. (Eds.), Ethnobiology and Biocultural Diversity. University of Georgia Press, Athens, GA, pp. 21–30.
Thayer, A.M., 1992. University technology moves to market vis patenting, licensing. Chemical and Engineering News August 24;17–21.
United Nations, 2005. Millennium Ecosystem Assessment. New York, NY, May, pp. 219, available at www.millenniumassessment.org.
United States Census Bureau, 2005a. World Population Clock. Washington, DC, May, available at http://www.census.gov/cgi-bin/ipc/popclockw.
United States Census Bureau, 2005b. World Population 1950–2050. Washington, DC, May, available at http://www.census.gov/ipc/www/img/worldpop.gif.
United States Census Bureau, 2005c. International Data Bank—Rank Countries by Population. Washington, DC, May, available at http://www.census.gov/ipc/www/idbrank.html.
United States Food and Drug Administration, 2005. Approved New Molecular Entities (NMEs). Washington, DC, May, available at http://www.fda.gov/cder/rdmt.
Zhang, Y.-B., Wang, J., Wang, Z.-T., But, P.P.-H., Shaw, P.-C., 2005. DNA Microarray for identification of the herb of *Dendrobium* species from Chinese medicinal formulations. Planta Medica 69, 1172–1174.