

# Sustainable Medicines and Global Health Care

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## Key words

- medicinal plants
- green chemistry
- conservation
- sustainable development
- technology integration
- individualized therapy

## Abstract

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The global population has now exceeded 7 billion, and forests and other resources around the world are being irreversibly depleted for energy, food, shelter, material goods, and drugs to accommodate population needs. For most of the world's population, plants, based on many well-established systems of medicine, in either crude or extract form, represent the foundation of primary health care for the foreseeable future. Contemporary harvesting methods for medicinal plants are severely depleting these critical indigenous resources. However, maintaining and enhancing the availability of quality medicinal agents on a sustainable basis is an unappreciated public health care concept. To accomplish these goals for future health care, and restore the health of the Earth, a profound paradigm shift is necessary: *all* medicinal agents should be regarded as a sustainable commodity, irrespective of their source.

Several approaches to enhancing the availability of safe and efficacious plant-based medicinal agents will be presented including integrated strategies to manifest the four pillars (information, botany, chemistry, and biology) for medicinal plant quality control. These integrated initiatives involve information systems, DNA barcoding, metabolomics, biotechnology, nanotechnology, in-field analysis of medicinal plants, and the application of new detection techniques for the development of medicinal plants with enhanced levels of safe and reproducible biological agents.

## Abbreviations

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GPS: global positioning systems  
NMR: nuclear magnetic resonance  
PCR: polymerase chain reaction  
UPLC: ultra-performance liquid chromatography

received Sep. 26, 2010  
revised Dec. 22, 2010  
accepted Dec. 29, 2010

## Bibliography

DOI <http://dx.doi.org/10.1055/s-0030-1270731>  
Published online February 9, 2011  
Planta Med 2011; 77: 1129–1138 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0032-0943

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## Introduction

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Future generations may well regard the period of 1850 to 2020 as one of devastating profligate utilization of much of Earth's non-renewable resources. It will be recognized as the "Era of Indescribable Waste", and we will be excoriated for our lack of consciousness and stewardship of Earth's resources by and for generations to come. We have not done well in our role of minding the Earth. The term "2020" is synonymous with clear vision. Maybe, by that time, we will have acquired the greater clarity to see what is needed and will have modulated our destructive habits, for the benefit of our descendants. This paper is a brief reminder that the fundamental sources of our medicines for the future must also be a part of that consideration.

The award of the 2008 Nobel Peace Prize to Al Gore, for his documentary "An Inconvenient Truth" and to the Intergovernmental Panel on Climate Change (IPCC), a unit of the United Nations established in 1988, follows a thirty-year period where there were increasing global concerns expressed with respect to deforestation, conservation, and renewable resources. The temperature modulations that are already observed in various oceanic and coastal regions around the world, or that are projected to occur in the future, are the direct result of human activity. The past 80 years or so have witnessed Earth's population increasing from about 2 billion in 1927 to over 7.05 billion today (October, 2010), resulting in tremendous pressures on those planetary resources necessary to maintain and enhance this ever increasing level of human activity and economic growth. Consequently, the central issue in climate change

is not emissions controls, pollution from non-renewable energy sources, carbon exchanges, or even developing alternative energy sources; those are outcomes of an apparently insatiable desire to procreate, resulting in staggering population expansion in almost every country of the world.

These continuously accelerating pressures on the resources of the Earth have resulted in significant losses of the primary forests worldwide. In addition, both mineral and marine resources are in steep decline, with the fishing industry in several areas of the world under serious threat. At the global level, perhaps there is no more important document on this topic than that published in April, 2005 by the United Nations (UN) as the Millennium Ecosystem Assessment (MEA) [1]. This document offers the clear warning that "...the ability of ecosystems to sustain future generations can no longer be taken for granted."

This statement from the MEA also relates to the global need for preparations, most of them based on plants, which have the power to heal. All drugs are ultimately derived from natural sources. Although medicinal agents are typically classified as drugs of natural or synthetic origin or combinations thereof [2], the synthetic components of drugs are derived through the ingenuity of synthetic medicinal chemists based on the elaborate transformation of chemicals from non-renewable, finite resources of natural origin, oil or coal. Estimates of the duration of these essential assets are variable. Yet, in considering the future, the need for accurate resource estimates is critical for planning purposes; for there is this persistent myth that the resources will "last" for generations to come. Thus, for the availability of all drugs, a critical issue is how long will the oil "last" at a reasonable cost, or have we already passed the "tipping point" where demand significantly outstrips production [3]? In addition, there are serious issues that relate to the air and water pollution, and the continuing effects on global warming, that are the result of the processing of coal resources for various purposes, including the synthesis of medicinal agents. Strategically, should we be relying long-term on non-renewable resources, which can be used over all the millennia only once, for the basic health care of an ever expanding global population?

All of the food that is consumed by the population of Earth each day is natural. We have learned over the millennia to grow both essential and exotic foods in a sustainable manner. Except for a minority of tribal communities, hunter-gathering for food is no longer widely practiced. Yet, for the medicinal plants used in primary health care, that remains the dominant cultural practice worldwide. Terrestrial plants, for food, for construction, for paper, and for a variety of other human needs, or for medicines, even when cultivated in the simplest manner, are a renewable resource. However, as with climate change, the pressures on Earth's ecosystems to create habitable space for humans and for their basic needs of food and shelter are the result of staggering population growth; they are not the cause itself. To this point, the discussions that have occurred on these topics are similar to applying a bandage for the loss of a limb. Unlike the leopard gecko, however, which has the ability to regenerate a tail when it is lost, regenerating the depleted resources of the Earth is not possible. Each barrel of oil or ton of coal is unique, and we are granted only one opportunity in the history of the Earth to utilize it responsibly. It is therefore important that the discussions of our present impact and the future priorities for Earth's non-renewable resources continue at all levels of societies across the globe, if only to emphasize the terrible outcomes that humanity will face if we do not modulate our practices after first rethinking our views

and our choices, personal and corporate [1]. Now it is essential to add the long-term access to medicines for a global population to that discussion.

## Sustainability and Resource Use



Awareness of the need to maintain and monitor Earth's resources has grown in recent years. The term "sustainability" was introduced as a concept to recognize and emphasize that, as a global society, there is a critical need to reconsider on a continuous basis whether our individual and collective actions result in the permanent depletion of the resources of the planet. In 1987, the UN World Commission on Environment and Development issued a report "Our Common Future" [4], also known as the "Brundtland Report". It provided a definition for "sustainable development", namely, "Sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs". Medicinal agents must be a part of this development. Discussions at the highest levels of the United Nations agencies, including the World Health Organization (WHO), the United Nations Industrial Development Organization (UNIDO), the Food and Agriculture Organization (FAO), etc., are needed for these future strategic directions. Synthetic medicines, even a simple aspirin, are not, and never will be, the core primary health resource for the majority of the people of the world. Traditional medicine, based on plant materials and enhanced by evidence-based research is, and will remain, that lifeblood resource on which communities around the world will be forced to rely.

"Sustainability" is neither a goal, nor is it an end point, and there is no single "pathway" to be followed. Strategies towards medicinal plant sustainability will vary depending on many factors, including funding, available expertise and infrastructure. Successful initiatives will require innovation and human creativity for the benefit of future generations by limiting the contemporary depletion of Earth's resources [5]. However, given the stunning increases projected for global population levels in the next 30–40 years, "limiting" depletion may not suffice. A collective will is required to implement innovative and sustainable technology from the highest levels of government through the board rooms of the chemical and pharmaceutical industries to the scientists who ultimately will be responsible for the necessary innovations. This transition in thought and practice will be expensive, and subsidies to develop such innovative practices should be a shared government effort with academic and industrial enterprises. In making this transition, the sustainability of the whole operation must be examined, not merely the product and its fate.

An enhanced view of what sustainability means for the delivery of medicines in the future begins with the chemical and pharmaceutical industries. It is imperative that they acquire a higher moral and ethical leadership position which reflects maintaining and enhancing the quality of human life for the majority. At the same time they need to be seen as a credible and sustainable enterprise in society, one which does not compromise the activities, including health care, of future generations. In much the same way that a food is labeled now with nutritional value, the chemical and pharmaceutical industries in the future will have to establish and declare, what level of depletion of the Earth's resources a particular product represents. Some aspects of how synthetic drugs can be made available in a more sustainable manner are discussed elsewhere [6–10], and perspectives on

these considerations are embraced by green chemistry. For now, let us turn our attention to traditional medicine and its present and future role. From a global perspective it is presently the primary form of health care for most people in the world. That situation will not change very significantly in the near future. In this context traditional medicine is used as a universal term, embracing phytotherapeutics and certain dietary supplements, as well as the many systems of medicine based on plants, minerals and animals used in various parts of the world.

Several recent previous discussions from this author on the development of traditional medicines have focused on aspects of quality control, including safety, efficacy, stability, and plant drug-synthetic drug interactions [6,7,9–16]. These discussions have resulted in proposals for an initial plan for the comprehensive future quality control and development of the medicinal plants used in traditional medicine [6,7,9–11,14–17]. In this brief summary, selected aspects of some sustainability and quality control strategies involving the integration of contemporary technologies into medicinal plant development will be discussed. Although regarded as a human right by the United Nations, access to quality health care is an enormous public health global issue at the scientific, clinical, economic, political, and policy levels. It remains one of the primary issues which divides the world, the North from the South. As an example, there are massive differences between government per capita annual health expenditures, from \$ 3074 in the US, to \$ 88 in the Philippines, and \$ 4 in Burundi [18]. Similarly, and in terms of the delivery of medicinal agents, there are tremendous disparities between the numbers of western doctors and the number of traditional healers per 10000 population in many countries of the world. The quality of the health care that is associated with the different origins of medicinal agents is likewise extremely different, and is reflected in the vastly different regulations applied to traditional medicines and synthetic drugs. In May 2005, WHO published a summary of regulations applied to traditional medicines around the world based on a survey of all 191 member countries [19]. Only 53 of the countries who responded had some form of regulations in place. Unfortunately, there was no assessment made of the nature of the existing regulations with respect either to the safety or the efficacy of the traditional medicines, of the sustainability (wild vs. cultivated) of the medicinal plants being used, or indeed of the implementation of the regulations. This WHO global survey is presently being resubmitted by nations, and it will be interesting indeed to see how much change has occurred. For many people all over the world, even in urban areas, the quality of health care based on traditional medicine has barely changed in the last 4000 years of human development. This is clearly an international tragedy which reflects poorly on the highest levels of WHO where traditional medicine has almost no “voice” whatsoever. The absence of regulations for traditional medicine for most countries in the world of course stands in dramatic contrast to the situation with respect to the regulation of prescription products in the developed world.

Twenty-five years ago, a WHO-associated group provided a frequently cited guesstimate that 80% of the population in the developing world relies on plants for their primary health care [20]. As the natural resources for these medicinal agents become scarcer, and because of the long-term public health requirement of relying on plant-based traditional medicines, this strategically important number merits rigorous scientific determination on a global basis in order that more accurate assessments of continuing resource need can be made for future health care. Perhaps the

ongoing WHO Global Survey of Traditional Medicine will provide some clarifying information in this regard.

Economies are evolving in various parts of the world, and urban populations are increasing. As a result, the use of traditional medicinal plants may be modulated in favor of selected, accessible synthetic drugs. Consequently, for both synthetic and natural medicinal agents there is the need to have available more refined estimates of the level of non-renewable resources that are needed for sourcing those agents, and the tonnages of chemicals, solvents, reagents, catalysts, and medicinal plants that are required annually in order to support local health care systems. From such studies, the net amount of non-renewable resources used each year can be projected, and in the case of medicinal plants, the acreage required for cultivation or the levels of imports established. The contemporary practice of the extensive wild-crafting for medicinal plants of commerce cannot be a long-term strategy for primary health care, recognizing also that socially and economically this is a complicated issue in which medicinal plant collection is an important aspect of subsistence living for many people in the world [21].

For drug discovery and development for the diseases that predominate in the less-developed world there is also a “great divide” [22]. Of the 1556 new medicines approved between 1975 and 2004, only 1.3% were approved for diseases prevalent in the less-developed world, including tuberculosis [23]. Almost no major pharmaceutical company has a commitment to drug discovery for tropical diseases, and in the revamped priorities of the major pharmaceutical companies, following the recent downsizing and realignment of their research programs, the diseases prevalent in the South, for which there are no or minimal accessible treatments, do not appear [24]. Given the limited number of countries with integrated pharmaceutical systems, the implications are therefore simple and clear. In a less-developed country, the government, together with the local academic and pharmaceutical institutions, will be responsible for the provision of medicinal agents for local diseases [6,7,9–11,15,16]. Thus, while a number of countries see their rich biome as “green gold” and regulate access to their biodiversity with some fervor, in practice, the major pharmaceutical companies have essentially no interest in developing those resources for new drugs. It will therefore be the obligation of most countries of the world to weigh the public health and economic issues of whether it will be more effective to develop local resources for the production of selected synthetic medicinal agents, to rely on imported drugs, or to establish research and possibly discovery programs, based on indigenous resources, to explore traditional medicines as a health care resource. In several countries of the world, those programs have already been initiated.

From the perspective of medicinal agents, health care in the future will be a blended mixture of allopathic medicine based on synthetic and natural drugs, and traditional medicine based on plants and fungi in a somewhat integrated system. There will be those people in a particular country who use, by choice and economic option, only the allopathic system, and there will be those who, based on necessity, will have access to only the local traditional medicine system. In between will be those people using, to a greater or lesser extent, traditional and allopathic medicines in a blended system of health care.

As mentioned, there is an increasing need to establish accurate estimates of the non-renewable resources required each year to produce synthetic and natural drugs and traditional medicines and their derived products. The total, non-renewable chemical

resources required on an annual basis by the major pharmaceutical industries of the world to produce synthetic and semisynthetic drugs have not been calculated. Attempts to access such information have thus far failed. However, as global accountability at the corporate level for the depletion of non-renewable resources increases, the pharmaceutical industry will be under increasing international pressure to make these data available, and to modulate their practices for a measurably different “greener” drug production. For traditional medicine the situation is quite different.

Many medicinal plant materials are gathered and used locally. They frequently provide a meager family income, particularly for women, through sales at a local market. Other medicinal plants and the products derived from them are significant entities in global trade. Over 400 000 tonnes of medicinal and aromatic plants are in global commerce each year, involving possibly as many as 53 000 plant species [21]. Depending on the country, up to 90% of those materials are harvested in a non-sustainable manner. Consequently, as the global population and their health care demands increase, in part because of increasing longevity [25], the native habitat is further pressured when indiscriminate collection, not cultivation, occurs, or when global commercial demand accelerates. There are over 28 000 plants on the Convention on International Trade of Endangered Species (CITES) lists [26], but the number of medicinal plants is not known, and thus it is not possible at the present to examine that impact on future health care.

Commercial purveyors of medicinal plants in many countries face a moral conflict because some of the best-selling products, (e.g., black cohosh, goldenseal, and American ginseng) are also at the top of the “at-risk” plant list [27]. Should retailers continue to sell those products? Some retailers in the US have made the choice to cease sales. In order to clarify the plant status to ecologically concerned patients, are certification standards needed for cultivated and wild-crafted plant materials? Undoubtedly, at some point in the future, manufacturers will be required to indicate both the plant sourcing and the CITES status on the package label. Which leads to the consideration of how and when does a government intervene to provide stricter regulatory control in order to prevent the loss of critical medicinal plant species, promote appropriate cultivation strategies as a part of ecological and economic development, and assure continuing access to medicines to maintain public health?

Low throughput clinical screening of plants thousands of years ago, and continuing today, established the requirement to assure the continuing availability (sustainability) of important medicinal plants as a health care resource for the community [28]. More recently, concern over the future availability of medicinal plants locally, regionally, and nationally has intensified. India has shown significant concern regarding the conservation of its medicinal plants, and there are many efforts underway for the conservation and preservation of important Ayurvedic, Unani and other medicines [29]. As many as 15 000 of the estimated 45 000 plant species of India may be used medicinally, of which more than 90% are obtained through harvesting in the wild [30, 31]. Additionally, between 4000 and 10 000 medicinal plant species face local, regional or national extinction [32]. At the same time, the quantity of Ayurvedic plants exported keeps expanding, and in the period 2005–2009 more than doubled [33]. At the national level, several departments [34] and the Government of India Planning Commission [35] have initiatives to conserve and cultivate important medicinal plants. The State Government of Andhra Pradesh, hav-

ing about 1800 medicinal plant species in the State, is conserving the gene pool and promoting *ex situ* cultivation. It is attempting to halt the trade in illicit plants by enhancing public awareness, developing economic cultivation practices, reforesting degraded areas with medicinal plant species, and creating a databank of existing medicinal plants in the wild [36].

For Africa, the issues of plant usage, species traded and the need for conservation and management have been discussed [37]. In southern Africa, where there are 130 000 medicinal plant traders and 200 000 traditional healers, and the medicinal plant trade represents 20 000 tons of plants worth \$75 million, the market, and livelihoods of traders are significantly threatened by excessive wild-crafting [38]. Strategies which have been proposed to address these conservation issues include: i) identifying medicinal plants under threat, ii) preserving the indigenous knowledge in order to retain medicinal plant diversity, iii) supporting local nurseries which propagate medicinal plants, and iv) promoting public awareness of medicinal plants, their conservation, and their biodiversity. A project on the development of the medicinal plant *Prunus africana* on Mount Cameroon is a recent example of efforts underway [39]. It is important that these models for medicinal plant conservation and sustainability are examined for their ability to be transferred to other countries.

### Traditional Medicine Quality Control

▼ The WHO Traditional Medicine Strategy 2002–2005 [40] places an emphasis on safety, efficacy and quality as one aspect of a four-part strategy to improve traditional medicine globally. The need to develop guidelines for safety, efficacy and quality is indicated as a fundamental precursor to establishing the evidence base for traditional medicine. Without a strong evidence base, traditional medicine will not be a reliable source of primary health care and will not be accepted as an integral part of a health system. The strategy also indicates a need to promote the sustainable use and cultivation of medicinal plants as a component to assuring access to health care. But what is a “quality” traditional medicine, and how can that be achieved?

Even though we are in the early part of the 21st century, there is nowhere in the world where there is adequate quality control of the traditional medicines that are used in primary health care. This is another aspect of the “great health care divide”. The regulations and requirements for a prescription drug to receive United States Food and Drug Administration (USFDA) approval for marketing and for post-marketing surveillance are extremely strict (albeit not infallible). However, in the USA and in most of the rest of the world, there are only minimal or no quality control requirements for a plant-based dietary supplement or traditional medicine to be marketed, even in relatively integrated health care systems. In Europe, the EMA has introduced the concept of traditional herbal medicinal products which requires 15 years of registration or notification in the European Union and 15 years outside Europe. In addition, the European Pharmacopoeia has adopted selected herbal monographs from the Chinese Pharmacopoeia. Neither of these steps addresses the integrated issues of quality, safety and efficacy as a clinically assured outcome.

There are numerous reasons why this situation still pertains. Inadequate funding as result of a low-profile for plants as a basic health resource in many societies is certainly one of the primary reasons. The absence of trained personnel who know the subtleties of medicinal plants and can implement adequate quality con-



trol standards is certainly another. The financial incentives on all sides of the medicinal agent industry are absent. Finally, changes regarding quality control can only arise from government policy decisions leading to laws and regulations, and that remains an on-going, very low priority process in most parts of the world. Policy makers are also reluctant to act because they, like many people, believe in the four “myths” regarding traditional medicine. It is now time to “bust” those myths. Perhaps one of the most dominant myths one encounters is that of safety and efficacy (more properly “effectiveness”) based on historical use. It is frequently expressed, even by experienced natural product scientists and traditional medicine clinicians, that because a particular plant has been used for hundreds, or perhaps even thousands, of years, that it is both safe and effective. The argument is made very strongly that if it did not have those attributes, it would not still be recommended and/or used. Another myth, frequently found in the public domain, is that traditional medicines and dietary supplements/phytotherapeutics ARE well regulated. Most patients are unaware of the quite different reality. There is also the myth among both scientists and regulators that using the “right” or “correct” plant or plant part for a traditional medicine or dietary supplement constitutes adequate quality control. Finally, there is the myth that an older, dried medicinal plant has decreased biological (therapeutic) activity, when in fact the opposite could also be the case. Unfettered claims and unfounded assumptions, such as the myths described, need to be firmly resolved in science. As a profound public health issue, they require a well-defined research basis.

Typically though, the patient is buying “blind”. After all, what is really in that package? Faced with an array of twenty products of a given plant from various manufacturers, what can the patient do? How can they choose a product which they know will “work”? Clearly that is impossible in nearly all of the present health care systems around the world. Even the simplest quality control issue of “how old is the plant in the product?” is not regulated or mentioned in a pharmacopoeia (if there is a pharmacopoeial listing). Globally, the system for making traditional medicines and phytotherapeutics available is based almost entirely on trust, that the product is what the label says it is, that it is safe, and that it will “work”. This is an entirely unacceptable public health care situation which affects us all.

Our vision must be [9,10,14,15,17] that the quality control of traditional medicines and phytotherapeutics is based on evidence derived from the highest levels of contemporary science and technology. It is, after all, the maintenance or improvement of the health of human beings that is at stake, and that right to life is within Article 3 of the Universal Declaration of Human Rights of the United Nations. Long-term, and underpinning all facets of the quality control of medicinal plants, is sustainability as a fundamental aspect in assuring continuing access to affordable medicines for the majority of the people in the world.

There are four fundamental “Pillars” for the quality control of traditional medicines and phytotherapeutics: i) information systems, ii) botany, iii) chemistry, and iv) biology. The last few years have seen dramatic enhancements in the level of science and technology which can be utilized in each of these areas.

Over the millennia, humankind has collected and recorded how innumerable plants may be used in health care to prevent and treat disease. From the earliest writings by the Sumerians on clay tablets, to the books by Chinese, Arabic, Greek, Roman and Korean scholars, through to the compilations of scholars in Europe in the Middle Ages, medicinal plant use has been passed on through

generations. Such information, in many indigenous medical systems, has also been passed on, from master to apprentice, through demonstration and the oral tradition. Only a portion, perhaps even only a small portion, of this oral tradition has been documented. More recently, medical anthropologists, ethnopharmacologists and botanists preparing herbarium specimens have described and compiled the uses of plants in medicine. Under the Convention on Biological Diversity, this yet to be recorded indigenous knowledge is a sovereign treasure, for which right to access requires permission from the designated government agency and the carrier of the knowledge [41].

All of these compilations of ethnopharmacological information are highly scattered in the literature or are in books available in very restricted locations. The volumes may be written in ancient languages, interpretable now to only a scholarly few. The medicinal value of this collected knowledge is immeasurable and should be extended and more widely disseminated as a global health benefit. However, there is no single place or group in the world where the information on the ethnomedical use of plants is being collected, collated, analyzed, and used as a resource for medicinal plant development [9–11, 15, 17, 42]. This constitutes a significant global health care tragedy which may be regretted in the future. It is the collection of this information, of the distribution, the usage, and the recorded preparation, the effectiveness and precautions associated with medicinal plants, that is an important aspect in justifying the conservation and sustainable development of common, threatened, and endangered medicinal plants. Such accumulated knowledge will also assist in balancing the desire for dissemination and evaluation of the information with the indigenous rights of the owners of such knowledge.

The development of local or national compilations of data of the breadth and depth of extant biological resources and of their known uses is absolutely critical at this time. Leading the world in this regard has been India, which has compiled the best assessment of the contemporary status of their plant and animal resources as published in 2006 in the *Jeeva Sampada* (wealth of bioresources) [43]. This effort should serve as a model and an inspiration to other countries to compile their own information systems on country-wide biodiversity and its uses.

Plant-based traditional medicine relies on the appropriate identification of a plant and the correct use of a plant part. There is an inherent and underlying assumption (actually another “myth”, which is rarely spoken or questioned) that the biological effects of the plant will be consistently reproducible. For reasons which will be explained subsequently, there is now a more fundamental concern: namely, what is a “plant”? Perhaps this may be thought to be a naïve question, but as consideration is given as to what constitutes quality control for a medicinal plant, this question and the implications involved, become of central relevance. Many regulatory systems for traditional medicine, including pharmacopoeial and formulary definitions, begin with a Latin binomial for the plant and naming the plant part(s) to be used. In the past, that was probably an adequate scientific response. Coupled with macroscopic and microscopic evaluation and simple chemical tests, the binomial has served as the name for the description of a plant for almost 260 years since the publication of *Species Plantarum* by Linnaeus; and it was the very definition of pharmacognosy as a discipline in pharmacy [44]. Recently, chemical profiling, including high-performance thin layer chromatography, and chromatographic assays, including high-performance liquid chromatography and gas chromatography, have been introduced for standardization in the European Pharmacopoeia.

That fundamental approach to defining a plant is now being challenged by two new technologies. DNA techniques, such as random amplified polymorphic DNA (RAPD), amplified fragment length polymorphism (AFLP), and inter-simple sequence repeat (ISSR) analysis have all been used to study genetic variation in plants, including medicinal plants [45], such as the antidiabetic plant *Momordica charantia* L. [46]. More recently attention for plant identification has turned to DNA barcoding [47], as one aspect of the Consortium for the Barcoding of Life. Although at present only about 72% accurate, it may eventually provide highly automated, hand-held devices for plant identification which could access large gene databases and provide almost instant identification [48]. The technique has already proved useful in medicinal plant species identification [45], including within the genera *Dendrobium* [49], *Hypericum* [50], *Aconitum* [51], *Phyllanthus* [52], *Panax* [53], and *Curcuma* [54]. Medicinal plants in the Polygonaceae [55] and Fabaceae [56], as well as Ghanaian antimalarial plants in markets [57] have been studied.

The second technique which is changing the way that a plant is defined is principal component analysis (PCA) of the low-molecular weight (ca. 200–500 daltons) compounds present in a plant sample, metabolomics [58]. Together, they would suggest that within a recognized plant “species” there are likely to be many “forms” or “chemotypes” (varieties is not an appropriate term in this regard), which will have different genetic profiles, biosynthetic capacities, and therefore chemical profiles. One can anticipate that within the next few years DNA barcoding, and probably PCA, will become essential aspects of all medicinal plant identification and integral to the pharmacopoeial identification of a plant.

The biosynthetic capacities for a given compound or series of compounds will not be constant for a medicinal plant. Catabolism of secondary metabolites will also vary. As a result, the concentration of an active constituent (or group of constituents) is likely to vary dramatically throughout a season [59]. It is also well established that the chemical profile of a plant is altered easily by a number of intrinsic and extrinsic factors. Plants grown under different conditions of soil pH, altitude, sunshine, moisture, etc., are almost guaranteed to have quite different chemical profiles. Attack by external factors such as fungal infestation will also lead to a modified chemical profile through the production of allelochemicals. In all of these instances, a modulated chemical profile is likely to significantly alter, positively or negatively, the concentration on a dry weight basis of the active constituent(s). Such changes are also likely to have an effect, which could be either positive or negative, on the concentration of any toxins that are present. As a result, both safety and efficacy may be altered. Consequently, defining a medicinal plant based on a Latin binomial and regulating the appropriate part to be used, does not in any way assure chemical equivalence to a quality control standard, or to a defined level of biological activity. Therefore, the anticipated health care benefit for a given weight of dried plant material is not assured either.

Medicinal plant collection conducted indiscriminately is not a sustainable practice for continuing primary health care. In part to ameliorate this situation, the WHO published the “WHO Guidelines for Good Agricultural and Collection Practices (GACP) for Medicinal Plants” in 2003 [60]. The document, also available online, offers suggestions regarding quality assurance, the formulation of national and/or regional GACP guidelines, and encourages and supports the sustainable cultivation and collection of medicinal plants. At the World Organic Trade Fair [61] in 2007, a

new standard for the collection of medicinal plants was elaborated. The International Standard for Sustainable Wild Collection of Medicinal and Aromatic Plants (ISSC-MAP) was developed by several German government agencies, industry associations, nongovernmental agencies, companies, working cooperatively with TRAFFIC, the wildlife trade monitoring network. Based on six principles, the standards include the maintenance of plant resources, licit compliance with local access requirements, the deployment of responsible management and business practices, and the prevention of negative environmental impacts. In addition, the Medicinal Plant Specialist Group within the International Union for the Conservancy of Nature (IUCN) Species Survival Commission [62] publishes *Medicinal Plant Conservation*. This important newsletter discusses a variety of issues, and presents studies and conservation strategies related to the sustainable use of medicinal plant species.

As well as cultivation, there are some alternative strategies to preserve important medicinal plant resources, although their implementation will typically result in a regulatory issue of reestablishing safety and efficacy. For example, it may be possible to seek alternative sources for the desired active constituent(s) through plant part substitution (e.g., leaves vs. roots), within the same plant genus (perhaps a more common plant), or, if the active principle is characterized, for plants with the same or similar constituents. A group in South Africa used this approach to try to substitute the aerial parts of several *Cryptocarya* species, rather than use the bark of the rare *Ocotea bullata*, both in the Lauraceae, as a cyclooxygenase inhibitor [63]. Where a non-sustainable plant part, such as the bark, root, or rhizome, is the medicinal plant part, research programs are needed to assess whether renewable plant parts or alternative plant sources can be made available. It is inappropriate to assume that all parts of a medicinal plant are “safe” or “effective”, based on the long-standing use of one plant part. Under these circumstances of substitution or replacement, assuring safety is a very serious issue requiring reestablishment scientifically. The replacement plant or plant part may be biologically effective, but it will undoubtedly contain many other constituents which may present a very different toxicity profile. Recognizing that each plant part has a very different chemical constituency profile necessitates that safety and efficacy must be reassessed *in each instance* prior to rational replacement.

A perhaps more subtle aspect of sustainability is the scientifically *justified* inclusion of each individual plant in a multicomponent preparation. This may be illustrated in the following manner. If a particular traditional medicine prescription is comprised of twenty individual plant materials, scientifically, it is appropriate to ask if all twenty plants are required for effectiveness. If it is determined that only four or five of the contained medicinal plants are necessary for effectiveness, the remaining plants can be omitted, thereby releasing those plant materials for alternative remedies. Such considerations for a more sustainable product profile also apply to determining the optimum harvesting time for biological effectiveness, and refining the dosing regimen based on a demonstrated level of biological activity on a batch to batch basis. One of the fundamental myths, mentioned previously, in medicinal plant usage concerns whether a plant material loses activity on extended storage as is often assumed (a popular myth). From the aspect of sustainability, correlating biological effectiveness with the post-harvest storage time (of the dried plant, of a plant extract, or of a finished product, such as a capsule or tablet, of lyophilisate) could reduce wastage of plant resources. In the past

this was a poorly researched area, with both loss of biological activity [64] and retention of activity over extended time periods [65,66] being reported. Stability studies on medicinal plant preparations are therefore of significant importance from a public health care perspective as one aspect of their quality control. Another aspect of sustainability which requires dedicated analytical research concerns the methods of plant extraction used in many countries to generate a medicine, usually a decoction or a lyophilized extract. Typically, the plant material is extracted once under pressure with hot water, and the extract processed either directly into a storage carton or plastic bag for the patient, or lyophilized in a spray-drying apparatus. What remains in the plant in terms of biologically active constituents which are not being accessed for potential health care is unknown. The marc is usually sent to a landfill or used as fertilizer. There is a need to examine whether there can be more effective uses for the acquired plant material while respecting the traditional preparation and use.

### Other Technologies Impacting Medicinal Plant Sustainability

Because of the global tendency to assume safety and efficacy for traditional medicine, and also the underlying assumption that somehow the contemporary plant sources will remain available, the extensive technologies which could potentially be utilized to enhance the sciences behind a particular medicinal plant preparation are rarely applied [9,10,17]. The technologies include those for plant identification and expression of the genes for the biosynthesis of active compounds, to those for the detailed analysis of the chemical diversity of a plant species, to the identification of the ability of a plant or a mixture of plants to regulate human genes. In addition, there are specific technologies, such as remote sensing [67], which can be applied to optimize the field collection of both wild and cultivated medicinal plant species. Introduction of some of these techniques as a field practice would invert the current strategies of bringing plants to a laboratory for botanical, chemical, and biological assessment [6,9,10].

Medicinal plants are under threat from over-harvesting in several parts of the world. However, there are relatively few initiatives underway which would preserve these important genetic resources for future health care. Few countries in the world have sought to establish medicinal plant conservation areas, gene banks, or systems for medicinal plant propagation. In Brazil, due to excessive wild harvesting, there developed an urgent need for cultivation programs to maintain the supply of *Pilocarpus jaborandi*, the source of pilocarpine [68]. In India, the Department of Biotechnology has established three national gene banks for the conservation of medicinal and aromatic plants [30]. They have also initiated several projects on the *ex situ* micropropagation of local species of medicinal importance. These are exceptional cases, and much higher levels of activity are needed elsewhere in the world to protect and propagate plant species of medicinal importance.

There is also a fundamental need in most countries which rely on medicinal plants as an integral aspect of their health care systems to determine the breadth and depth of their medicinal plant resources. Where are those resources in the wild, and how can they be measured and monitored? These are obviously critical aspects of their sustainability. Trends in medicinal plant populations, particularly those which might be challenged in coastal areas

where climate change may impact their continued growth will evolve as an important survey activity.

The original locations of medicinal plants can be mapped using global information systems (GIS). Many herbarium and botanic garden websites now include information from the original accession site in the form of maps which can indicate the original location of the acquisition. One future strategy to learn more about the (admittedly past) locations of an individual medicinal plant is to unify this information from the major herbaria across the world. Such an initiative, coordinated through a single website, could eventually offer the opportunity to determine and map (with varying degree of specificity depending on the herbaria notation) the original location of every herbarium specimen collected. It would represent an invaluable and long-lasting resource for medicinal plant conservation and cultivation. Disseminating online the resource locations of the medicinal plants of importance for global health care is a critical need for the future. It is recognized, of course, that these are historical data. They cannot account for recent changes in distribution or access which may have occurred since specimens were originally collected. Integrating the respective data from Google Earth would provide some indication of where potential resource locations may have already disappeared due to urban development or other factors. Contemporary, in-field based information is therefore critical in addressing local needs, now and for the future.

India is also leading the way in providing access to aspects of this information. Through the Ministry of Environment and Forests, the Foundation for Revitalization of Local Health Traditions (FRLHT) has developed 54 medicinal plant conservation areas in southern India, and GIS maps of the distribution in India and neighboring countries of the 960 species traded and of 7637 additional medicinal plant species are available [69]. GIS data are also behind other efforts [70] to map the distribution of medicinal plants for conservation purposes elsewhere in the world.

Local, experienced, plant collectors “know” through traditional practices, when to collect a particular medicinal plant. However, given the significant metabolic dynamics that have been established for the biosynthesis of active plant constituents, it is important, from a conservation perspective, to harvest both wild and cultivated medicinal plants at a scientifically established point in time which optimizes safety and effectiveness. This will assure that plant usage is maximized and the sustainability of the plant enhanced. How might optimum harvest time be determined, and are there new technologies which can be applied? Although not a “new” technology, there are also remote sensing techniques whose use should be expanded for medicinal plant evaluation.

For almost 35 years, lasers have been used for the remote (stand-off) sensing of compounds and plants [71]. These techniques have included Raman spectroscopy [72], near infrared Fourier transfer-infrared (FT-IR) spectroscopy [73], and attenuated total reflection FT-IR (ATR/FT-IR) spectroscopy [74]. Although agriculture and viticulture have utilized various spectral techniques for the determination of when crops are ready for harvesting, etc. [67, 75], hyperspectral imaging of medicinal plants is just beginning. Using silver-coated glass fiber tips, surface enhanced Raman spectroscopy (SERS) analysis has been conducted [76], and the alkaloids in crude plant materials have been studied with a micro-Raman spectroscopy technique [77]. ATR/FT-IR and FT-Raman-spectroscopy have been used to study the alkaloids in *Papaver somniferum* (opium) capsules [78]. Cocaine has been identified using a fiber optic Raman probe and portable Raman spec-

trograph [79] and the presence of cocaine in mixtures has been studied using near-IR Raman [80]. A recent review has summarized some of these research activities [74]. It is expected that once there are identified active (or marker) compounds, an expansion in the use of remote sensing techniques for optimizing medicinal plant collection will take place. Integrating these technologies into hand-held devices will allow for a quite innovative strategy for quality control of medicinal plants.

In plant-based drug discovery and traditional medicine evaluation, the dried plant materials are invariably brought from the field to the laboratory for processing, extraction and analysis. The use of remote sensing technologies for evaluating medicinal plants is one example of what should become a trend in the study of the bioactive constituents of medicinal plants – taking the analytical laboratory to the field and conducting botanical, chemical, and biological evaluations in that location. This concept has been termed by the author as “pharmacognosy in a suitcase” [7, 9, 10]. The techniques would integrate multiple, diverse electronic and nano-technologies into a field-based, portable instrument laboratory. As such it will enhance medicinal plant research in the field, and permit a rapid determination of the importance of plants as potential medicinal agents. Furthermore, it would assist in efforts to examine the conservation and sustainability of medicinal plants, to identify new areas for drug discovery and quality control research, and could directly enhance local health care practices in traditional medicine.

There are a number of significant questions relating to medicinal plants that, with the appropriate technologies, could be addressed with such an integrated system. These questions include: i) Where is it on Earth that we are collecting medicinal plants? ii) What is the accurate identity of the plant? iii) If the plant has been studied previously, is it likely to contain chemical constituents of significant interest? iv) At the time and location of study, does the plant sample possess the anticipated activity, or alternatively does it possess other activities of interest? Finally, v) How does this new botanical, chemical, and biological information relate, wholly or in part, to prior knowledge of the species?

There are a variety of critical technologies to be incorporated into an integrated system. Solar-powered (in clothing), satellite-linked, micro-GPS and a selection of normal vision and IR cameras (and hyperspectral imaging depending on need), remote sensing technology for the identification of selected compounds, a mini-PCR instrument, micro/nano-extraction and separation techniques, the ability to conduct gene based profiling, a mini-UPLC and mass spectrometer, and data acquisition, processing, and transmission systems. Integration of these technologies into a functional operating system is the challenge to be addressed.

On-site, unambiguous, DNA-based, identification of plants is essential. Nano-technology-based, mini-PCR machines are available [81] and could provide a rapid gene profile of a plant. Given the rapid progress in DNA barcoding of plants [45, 47, 48], it is clear that this will be a powerful laboratory and in-field technique to characterize medicinal plant DNA. Comparison with databases on site, or through satellite communication, should permit almost immediate plant identification, and, in combination with data from prior PCA analyses, offer a quite well-developed chemical profile. Hollow-fiber systems have recently been described for plant extraction and processing [82], and these techniques could be expanded to search for specific bioactivities. Using a multivalve matrix, and moderate pressure chromatography for initial processing, should afford microliter samples suitable for further analysis.

A gene profiling system involving either whole or partial human genome arrays which can determine, through gene modulation, the mechanistic effectiveness of a medicinal plant on a reproducible basis, will be an essential tool for field work. Although relatively few studies of the gene modulatory effects of medicinal plants have been published thus far [83], one can anticipate that in the future there will be databases available for compiling and correlating the modulations induced by the major medicinal plants. This will allow for the in-field data from a plant of interest, or a new plant, to be biologically compared. New mechanisms of action for medicinal plants will be disclosed in this manner which will lead to the development of designer traditional medicine products.

Global access to very large databases will be essential for real time field operation; including those which i) contain DNA profiles and barcoding data on plants, ii) report the location and occurrence of specific plants based on the acquisition of global positioning information from existing herbarium samples, iii) analyze the uses of a specific plant as a traditional medicine on a global basis, and iv) can provide chemical, biological and clinical summaries for plants and their constituents.

The biological activity of a medicinal plant is based, for the most part, on the range and type of small molecules contained in an extract of the plant. The ability to be able to quantify this array of molecules in a dynamic manner is called metabolomics. It provides a rapid technique, superior to other post-genomics technologies, which can provide pattern recognition analyses of a plant extract. Once the active principle(s) are known in the plant, the metabolic profile can then provide significant information on the anticipated biological activity of the sample. When data from the analysis of several samples of a given plant are available, the application of principal component analysis (PCA) can rapidly reduce very complex data sets, such as NMR analyses, for a plant to a single point, and based on similar chemical profiles clusters appear. When these clusters can be related to a biological effect it can be seen that the chemotypes of a plant can be identified and a correlation made to a chemotype which is likely to have a higher level of a desired biological effect. In this way, medicinal plant cultivation can focus on that specific chemotype of the plant and provide a more sustainable resource for a continuous health benefit. One is reminded of the situation with *Cinchona*, and the quest for the high-yielding seeds for optimizing quinine production [84].

There are many different aspects of the application of biotechnology to the development, optimization and sustainability of medicinal plants, some of them discussed by Tripathi and Tripathi [85]. Perhaps one of the most interesting areas for potential development in the future will be the possibility to “design” traditional medicines. Already, and based on clinical diagnostic experience, modifications are frequently made to both traditional Chinese, as well as Kampo, medicines as the result of a physician deciding to add or subtract plants from a particular formula. While there are obvious quality control and safety and efficacy issues with such a practice, it is an allowable practice. What is missing is the evidence base, and one can imagine that in the future, that it will be possible to formulate a traditional medicine prescription exclusively for the patient based on a determination of genome profiling and known gene modulatory effects of individual plants and perhaps even complex plant mixtures. This can be the systems biology impact on traditional medicine for enhanced health care.



## Questions and Conclusions

Earth is straining to support the health care requirements of a burgeoning population. While much attention has been focused on renewable energy resources and “green” chemistry, very little attention has been given to assuring the sustainable supply of both critical synthetic and natural medicinal agents. A selection of the issues relating to quality control and sustainability in medicinal plant research has been mentioned in this brief overview; a plethora of questions remain. Among these, the following are presented in no particular order of priority. How can we conserve and preserve the biological resources for the health and economic benefit of future generations? What are the implications of population growth and climate change for traditional medicine? How truly “sustainable” is plant-based traditional medicine considering the ongoing concerns of wild-crafting compared with cultivation? Would the demonstration and availability of safe and effective traditional medicines allay, in part, the impact of oil-based drug synthesis on global resources? From a patient perspective, what is the quality of the science behind the dietary supplement/traditional medicine being provided to the patient? Is there a feedback mechanism for relating evidence-based effectiveness to sustainable medicinal plant use? Should dietary supplements and traditional medicines be labeled for being wild-crafted or harvested? What is the continuing health care agenda for the next 15–20 years to make available safe, effective, and sustainable traditional medicine products globally?

The previous discussion has illuminated how the science behind traditional medicines can be enhanced with a long-term vision of assuring the sustainable production of critical plant species for the benefit of global human health. As Leonard Cohen writes, “There is a crack, a crack in everything, that’s how the light gets in” [86]. Perhaps this presentation will shine a light on seeing medicinal plants as a sustainable resource essential for the health of the Earth, and for many of the people of Earth on a daily basis. The goal has been to focus attention on establishing an evidence base for medicinal plants and for responsible health care, where assumptions are minimized and scientific evidence for safety and effectiveness is optimized as an ethical requirement. The integration of these ideas and other high-technology strategies will assure the global requirements for quality medicinal agents necessary to maintain and advance public health care. It is recognized that for most of the world, these “standards” may not ever be achieved. To place them as a goal on the pathway is valuable though, for even if small steps are made on the long pathway, human health care will have improved enormously.

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