



ECOPHARMACOGNOSY – WHY NATURAL PRODUCTS MATTER – NOW AND FOR THE FUTURE

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ABSTRACT

The new term “ecopharmacognosy” reflects the need to focus on the sustainable development of biologically active natural resources, now and for future generations. Conceptually, it provides both a philosophical and a practical framework through which techniques, applications, and scientific perspectives can be reconsidered and developed to enhance the sustainability and quality of products globally and assure beneficial outcomes. In this brief review, selected aspects of ecopharmacognosy in the future development of natural products for society, particularly for patient health care, based on a holistic approach to technology integration, are presented.

Keywords: ecopharmacognosy, traditional medicine, integrated technologies, future challenges

Introduction

Humankind is an integrated biological form of life on Earth. As humans, we use natural products in broad aspects of our lives; for shelter, food, resins, gums, waxes, flavoring agents, spices, perfumes, cosmetics, Rx and OTC pharmaceuticals, traditional medicines, herbicides, insecticides, and substances of abuse. Plant materials are therefore a major aspect of global health, whether that is personal health care as a patient (not a consumer!) or whether that relates to the health of the Earth¹. Only when a population is maintained in a healthy state can consistent economic and social development be linked to appropriate personnel and available resources². Long-term, a healthier society will promulgate national sustainable practices, rather than the unlimited growth of population and a continuously expanding economy. The former choice reflects a society where nature is revered and not abused or exploited, and where the effects of globalization directly benefit a local economy, not one on another side of the Earth.

However, there is a fundamental assumption that the plants or other organisms necessary to meet societal needs for any of the indicated uses will be available as and when needed. Who is responsible for assuring this? With a burgeoning global population rapidly approaching 8 billion, increased life spans, and the relentless depletion of natural resources, this assumption is now false. Consequently, new considerations for the sciences which underpin the long-term accessibility of natural products are urgently needed. Before discussing these, some additional background is necessary.

Fundamental to a healthy Earth is reducing population growth. Until the major religions actively support population control, Earth is on a shattering downward spiral of economic and environmental disaster. A one-minute glance at the population clock³, and the realization that those new humans will require vast resources for lifestyle maintenance

for probably 85-90 years, will convince that the scenario for global resources beyond 2050, let alone 2100, is not an optimistic one. Meanwhile, we must deal with our present reality. There are three mitigating factors for maintaining global health based on increases in population, climate change, losses of biodiversity and traditional knowledge, and time. Since the beginning of the industrial revolution in about 1760 in England, vast improvements in overall living standards, health maintenance, and economic, industrial, sociological, scientific, and technological achievement have occurred⁴. At what cost to the planet? We don't really know. There is an information deficit with respect to the achieving a full understanding in terms of loss of biodiversity, warming of the Earth's atmosphere, environmental degradation and pollution, and their short- and long-term impacts on global health⁵.

Scientific prognostication and available evidence indicates that rising air and ocean temperatures, more extreme weather, rising sea levels, and increasing levels of CO₂ will have a profound effect on many broad factors impinging on human health⁶. Among these are, enhanced parasitic vector ecology for malaria, dengue, Zika virus, etc., increasing levels of allergens causing respiratory distress, and the depletion and contamination of water supplies following natural disasters resulting in increases in internal microbial diseases. Are the medicinal agents, natural or synthetic, available in those vulnerable regions of the world as these outcomes unfold? As climate changes, various parts of the world are under the threat of experiencing negative impacts of either flooding, drought, or loss of sea coast regions. These factors will have a major impact on medicinal plants, since metabolic profiles will be modulated in unpredictable ways as their biosynthetic systems are stressed. It is already well-known that any change in environment (heat, cold, wet, dry, altitude, soil pH, etc.) is likely to afford a plant (e.g. ginseng) with unpredictable changes in the array of metabolites⁷.

What this may mean in terms of profiles for both medicinal and aromatic wild and cultivated plants is a mystery requiring profound research. The vulnerability of those resources within the general commodity (for aromatic and essential oil plants), and health care sectors (for medicinal plants) will necessitate assessment to maintain consistency and accessibility.

The staggering losses of biodiversity induced by human actions are only one aspect of the anthropogenic era¹. Extinctions of various forms of life have occurred over the eons of the existence of planet Earth. What is being witnessed now though is the unprecedented, human-driven destruction of the environment and its assets for immediate financial gain and profit without the consideration for future generations, a topic well-covered by the Rockefeller-Lancet Commission report of 2015⁸. Such profit-driven, economic growth is neither sustainable, nor necessary. Harmony with nature, and a realization of the interdependence of human beings and nature, are core assets for a sustainable planet. St. Hildegard of Bingen⁹ and Buddha¹⁰ long ago recognized this. Now is the time for humans, as the dominant sentient beings on the planet, to act consciously and positively to assure a sustainable future for Earth. Which, as sentient beings, brings us to "time".

Have we already passed the "tipping-point" of a sustainable Earth? If we have, then our contemporary and future actions are only an amelioration, a delaying effect on horrific outcomes. "Time is of the essence" is an old English aphorism. Two facets of time are relevant to this discussion: i) setting aside time, and ii) time running out. In terms of natural products and the resources associated with their development, few people these days set aside (create?) time to think and contemplate. We speak of "finding" time, an erroneous concept. Time is omnipresent. How we choose to use that time is critical. Newport¹¹ has suggested the term "deep work" for the process of contemporary reflective

thinking. When professional activities, the contemplation of your science in the future, are performed in a state of distraction-free concentration which pushes your cognitive capabilities to their limit, that is "deep work". Each of us, every day, is a witness to the barriers to such creative moments. We are involved with committee meetings, teaching, writing papers, grants, analyzing data, supervising students, traffic, Facebook notifications, Tweets, Linked In, e-mail alerts, literature, family, friends, pets, sports, political activities, hundreds of TV channels, Netflix, Hulu, Amazon Prime, etc., etc. Our world is rich in distraction and poor in "deep work". Yet, as scientists, we are being called to order by society, and as natural product scientists, we are being challenged to solve global issues relating to both food production and medicine availability in sustainable terms. Challenged, to redefine our societal purpose, our "function", *before* defining our form¹². The subsequent consideration of "form" serving as a more precise range of actual studies to be conducted. That challenge demands that we engage in "deep work", and there is no shortage of potential engagements!

In the broad sense, we need to determine whether there is a societal purpose for (eco) pharmacognosy. In the medicinal, cosmeceutical, nutraceutical, agricultural, and other sciences that operate globally, what is it supposed to do, and for whom, where, and how? Ecopharmacognosy is a well-established, diverse collection of sciences and technologies which operates at the cutting-edge. To what future ends? To whom has this expertise been offered, and for what purposes? Which industries? Which government agencies? Which global initiatives? For what will ecopharmacognosy be functionally responsible? We are like Alice on her Adventures in Wonderland over 150 years ago, when she first met the grinning Cheshire cat¹³, and famously asked, "Would you tell me, please, which way I ought to go from here?" To which the cat

replies, "That depends a good deal on where you want to get to."

Over 45 years ago a group of astronomers offered to examine the origins of the galaxies; the Hubble telescope was created and still transmits amazing images. Hence, we know more about galaxies zillions of miles away than we do about the medicinal plants on Earth. That is unacceptably ironic, demanding a response. As natural product scientists we need to come together for our own "Hubble" activity. Yet, are we prepared, in the profound, challenging complexities of humanity now and in the future, willing to accept an assigned role for natural product development? Absent a commitment globally, or even locally within a country, pharmacognosy will forever be mired at the junction of *status quo* and societal responsibility; enmeshed and amaurotic.

What then is "ecopharmacognosy", and what are its implications in this scenario? As explained in detail elsewhere¹⁴⁻²² the term was developed in early 2012. It was created, in part, to recognize the challenges addressed by the "Planet Under Pressure" Conference²³, whose "State of the Planet Declaration" called for a societal contract to encompass:

- global sustainability analyses based in science,
- integrated, international, and solutions-oriented research, implemented and involving government, society, scientists, and the private sector,
- enhanced dialog on issues of global sustainability.

Pharmacognosy is a global science founded on the judicious use of natural resources for societal benefit. Yet we have not addressed how we each have individual and collective roles to play in terms of "sustainability". Moreover, that philosophy and practice must be conscious and conspicuous components in our lives and in our work.

In 1993, a new, broad definition of "pharmacognosy" was developed as "the study of biologically active natural products"²⁴. Based in that definition, pharmacognosy is unlimited by the source of the studied material (plant, marine, microbial, insect, mammalian, etc.), or the research area (botanical, analytical, chemical, biosynthetic, biological, pharmacological, clinical, economic, legal, regulatory, etc.). "Ecopharmacognosy" introduces the concept of sustainability, and is therefore defined as "the study of sustainable, biologically active natural resources"¹⁴⁻³¹. It stresses the importance of sustainability in the field of natural product research from several quite disparate perspectives. Over time, it has evolved into both a philosophical approach, and a series of suggestions for "deep work" and for practice. In the following discussion, the focus will be on health care; the fundamental philosophy though is also applicable in many other areas of biologically active natural product development (fragrances, flavors, herbicides, insecticides, dyestuffs, etc.).

Philosophy and Practice

Most natural product research aimed at drug discovery or on understanding traditional medicines is based on at least thirteen myths¹⁷⁻¹⁹, including that the plant will always be there, and that it will be affordable for the patient. Ecopharmacognosy reverses the paradigm of translational science and operates from a patient-centered perspective, asking in the initial research stages: "What are the patient needs and expectations?" and "How will that be achieved?"

A patient desires a medicine that reliably heals, cures, or prevents. That agent must meet (inter)nationally defined standards of Quality, Safety, Efficacy, and Consistency. Furthermore, as mentioned, the product must be Accessible: available and affordable, to the patient, to a private insurer, or to a government as part of a national formulary. Thus, we can embrace the patient needs

as QSECA (cue-sec-a). In the future, how many patients will there be and what resources will be required to meet those needs? Who is studying that from a sustainability perspective? If, as projected, the global population reaches 10 billion by 2040, only 22 years from now, who is responsible for assuring accessibility to medicinal agents, synthetic and natural? How will the diverse health care demands induced by climate change be met^{20-22,25}? In addition to population increases, the complexity of this scenario is confounded and compounded by three factors: i) the globalization of existing traditional medicine systems and products and their use by an ageing population, ii) the development of new traditional medicine agents, phytotherapeutics, nutraceuticals, and cosmeceuticals, and iii) the vast "e-medicine cloud" of unregulated, plant-based medicinal agents. Each of these factors requires additional supplies of plant materials. From a patient perspective, how much of the evidentiary science to these products will fit the criteria of QSECA?

Typically, 80% or more of the medicinal plants used in traditional medicines and phytotherapeutics are wild-crafted, and some are even on lists of threatened plants^{26,27}. Thus, even the concept of studying those plants should be subjected to ecopharmacognosy considerations. For selected and prioritized traditional medicines of demonstrated safety and efficacy, more effort is needed globally to shift them from a "forest economy" to a "field economy"^{26,28-32}. In the absence of sustainable cultivation, the "disappearing" plants become the object of substitution and adulteration, and unethical commercial interests replace positive patient outcome considerations. Thus, to be societally relevant, ecopharmacognosy research requires "eco-centric" intentions, as a societal expectation.

There is an important gap, effectively a chasm, to be bridged that is almost a "Catch-22" situation³³; moreover, it lies at the very heart of the

precepts of QSECA. The "gap" is this. There is no economic system in the world which can develop prioritized traditional medicines into full-scale drugs to meet global health care needs. At the same time, synthetic drugs are not, and will not ever be, able to meet global health care needs. An abyss of patient health care neglect is the result in most countries in the world. A new approach to a patient-centered, risk-benefit assessment based on local needs and economic considerations is needed in many countries to enhance the quality of traditional medicines, maintain their accessibility, and address unmet health issues.

Our own deep work

With that background, let us return to our own "deep work" in ecopharmacognosy, for there is much to be considered and developed as time marches on. Some aspects of this process have been described in recent articles^{21,22}. We must evolve strategies on how to: i) investigate the impact of climate change on vulnerable medicinal plants, ii) respond to global health care "gaps" in drug needs which pharmaceutical companies cannot, and will not, fill³⁴, iii) respond to the losses of biodiversity and traditional knowledge, iv) enhance access to global information on natural products, v) change the paradigm and challenge conventional natural product thinking³⁵, vi) promote both collaboration and individuality to potentiate scientific outcomes, vii) make sustainable practice improvements^{17,18,21} and viii) translate the holistic research results (what traditional medicines work, what do not, how to standardize, etc.) to the regulatory system, the industry, the practitioners, and the patients³⁶.

This is a very onerous list of tasks for the coming years, and one aspect of a list of sixty challenges for the natural product sciences²². The good news is that many current practices already can be embraced as ecopharmacognosy practices; other practices remain to be implemented. Some examples include: i) testing organisms for biological

activity in the field^{18-20, 22, 25, 35, 37}, ii) studying only sustainable plant parts (leaf vs. bark material), iii) continuing the prioritized development of cultivated plants vs. those that are wild-crafted, iv) invoking more environmentally friendly extraction and separation procedures, including the development of reusable chromatographic materials, and v) minimizing the use of non-recyclable solvents. Other strategies involve: vi) construction of databases for dereplication strategies, vii) studies on the potential use of natural insecticides, herbicides, and dyestuffs, rather than non-sustainable synthetic agents, viii) expanding the use of cheap, natural, enzymatic reagents, such as commercial plants and vegetables, for organic synthesis³⁸, ix) developing medicinal or other uses for commercial food crops or their waste products^{39,40}, x) expanding the applications of *in silico* drug discovery to reduce costly biological screening⁴¹, xi) conducting genomic mining studies in microbial and plant resources to seek new drug origins⁴², xii) using biosynthetic knowledge to simplify microbial product profiles, xiii) simplifying, while maintaining the safety and efficacy, of complex traditional medicines, xiv) using network pharmacology to discover, *in silico*, known and available compounds for new applications^{43,44}, xv) reducing the time and regulatory steps to a marketable product for patients by developing simpler processes for assessing risk vs. benefit, and xvi) harmonizing regulatory standards to promote the globalization of evidence-based products, including developing pharmacopoeial equivalence³⁶. It is also important that we recognize as aspects of our portfolio the dark sides of ecopharmacognosy, namely the use of natural illicit drugs and the use of rare (or near extinct) animal products as unproven medicinal agents²².

Pathways for sustainability-based, patient-focused studies in ecopharmacognosy, should include the following:

- Developing traditional medicines, including their quality, safety, efficacy, consistency, and accessibility (QSECA), as an essential societal responsibility to systems of integrated health care.
- Fostering cooperation and collaboration between relevant sectors of the government, academia, and the manufacturing industry for a long-term, staged program of the development of expertise, information systems, and facilities, dedicated to the improvement of traditional medicines.
- Developing centers of excellence for the conduct of focused, highly collaborative and interactive research, and establishing rational risk-benefit based, decision-making protocols for prioritized traditional medicine studies based on local health care priorities.
- Committing to the conservation and agronomic development of medicinal plants to assure accessibility to traditional medicines as part of a program of medicines security.
- Establishing a continuum of reproducible biological assessment of standardized preparations of plants *in vitro*, *in vivo*, and in humans.
- Sponsoring clinical trials that are relevant to the projected use(s), and report in full both positive and negative results. Requiring pharmacovigilance for the interactions between traditional medicines, and between allopathic and traditional medicines, with global reporting.
- Promoting practitioner education as an essential aspect of translational traditional medicine.
- Fostering communication within and between the different systems of medicine to enhance the establishment of integrated health care system.

Following this path, ecopharmacognosy will stay relevant, be multifunctional, and can formulate far-reaching, patient-focused plans for a healthier, more sustainable society. For the future is about to change many paradigms.

World in 2030

In 2030, the global population will be about 8.55 billion, about 12.9% more than in late 2017. Fortunately, the population growth rate, currently about 1.12%, is projected to continue to decline from a high of 2.09% in 1968 to 0.88% in 2030. However, UN estimates indicate the need for 50% more food, 45% more energy, and 30% more water by 2030, than in 2012. Surprisingly, there are no estimates for the increase in medicinal agents that will be needed at that time, particularly given the vast increase in an aged population. By 2030 we will be much more fully connected (goods, services, power monitoring, etc.) locally, and globally. Robotics and automation (cars, trains, aerial transportation, daily processes) will be pervasive. Integrated information access and data processing and interpretation through hand-held or wearable devices, as well as interrelated laboratory equipment (automated structure determination) will be faster. Perhaps, most importantly, there will be the unknown factor of climate change, and its effects on economics, health, and quality of life.

Many aspects of the impact of advanced and hyphenated technologies on ecopharmacognosy in the future have been discussed elsewhere¹⁶⁻²¹. An important outcome of the influence of technology on ecopharmacognosy thinking involves the use of *in silico* services, database systems that may relate to the discovery and design of modified natural products given chemical space considerations at receptor/enzyme sites, or to the interpretation of data. In the latter instance, care must be taken to review the data from a natural product perspective. Examples are already available where "unnatural" compounds have been claimed as metabolites in various natural materials through a reliance on database spectral conclusions. Hopefully, by 2030 there will be a well-established series of integrated archives related to the botany, ethnobotany, ethnopharmacology, location, chemistry, spectroscopy, biology, pharmacology, and clinical

effects of natural product extracts and compounds, the Global Archive of Natural Products, available as an application for smartphone use²². The latter should also have the capacity for seamless interaction with other sensing devices for detection and analysis^{21,22,45,46} – the dream of ecopharmacognosy in a hand-held device.

"Dreaming" has a quite broad perspective in the future of ecopharmacognosy. As mentioned, a list of sixty challenges for natural products for 2030 was recently presented and the background partially discussed²². Those are dreams. A paradigm shift to a patient-centered approach for natural product research as a foundation of ecopharmacognosy is another dream. Assuring that "medicines security" has the same status at the World Health Organization as food security at the Food and Agriculture Organization⁴⁷ is a further dream. As John Lennon said "A dream you dream alone is just a dream. A dream you dream together is a reality". Together, let us make the philosophy and practices of ecopharmacognosy a reality.

Conclusions

Ecopharmacognosy, as a philosophy and practice, promotes consideration of sustainability in the development of natural products in health care, cosmeceuticals, nutraceuticals, and agriculture at an early stage. It encourages the study of sustainable natural resources, of processing procedures which require lower energy consumption, and of alternative sustainable strategies for organic synthesis using natural reagents. It supports the *in silico* evaluation and optimization of known available compounds as enzyme inhibitors, covalent binders and DNA intercalators, as well as the utilization of network pharmacology to discover potential biological activities for known compounds, prior to *in vitro* testing. This process conserves resources instead of requiring protracted isolation protocols or utilizing previously obtained valuable metabolites. Importantly, it promotes a patient-

centered approach to traditional medicine/phytotherapeutics in an integrated health care system, which is evidence-based in contemporary science, translated into practice.

Acknowledgements

The author appreciates the discussions and support from many friends and colleagues around the world concerning the philosophy and concepts outlined in this and related articles.

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