Ecopharmacognosy and the globalization of Traditional medicines

Geoffrey A Cordell
Natural Products Inc., Evanston, IL 60203, USA and Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL 32610, USA
E-mail: pharmacog@gmail.com

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“Ecopharmacognosy” is the study of sustainable, biologically active, natural resources. It provides a philosophical and practical framework for developing new strategies and scientific perspectives which can assure global healthcare product accessibility and beneficial outcomes. Here, the sustainable precepts of ecopharmacognosy to develop improved traditional medicinal agents for globalization, based on a holistic approach to technology integration, will be presented. Plants remain a primary source of healthcare for the majority of patients in the world. However, they are typically used with minimal quality control. In addition, there are many tropical diseases, as well as multidrug-resistant organisms, requiring drug discovery programs. To address these needs, ecopharmacognosy approaches and network pharmacology must enhance the quality, assure the safety, demonstrate efficacy, and provide consistency (QSEC), and explore the many diverse effects of individual and complex products at the gene level. Field-based instruments are being deployed to assess natural materials non-invasively, and spectroscopic and chromatographic procedures are in development to analyze quantitatively single and multi-component plant mixtures for established bioactive markers. Combining contemporary technologies and sustainability considerations, as aspects of ecopharmacognosy, are important strategies to enhance the quality control of traditional medicines for improved patient care.

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A man walks into a coffee shop and orders a cup of coffee. After sipping it, the waitperson asks him, “How does the coffee taste this morning?” “It doesn’t have to taste,” the man replies, “It just has to work”. Almost everything that needs to be known about traditional knowledge and its effectiveness and application from a healthcare perspective is in that simple repartee. The concept of patient-centering by the provider, of self-medication based on prior knowledge, of the taste not being a consequence, so long as the “drug”, in this case caffeine, actually works, and of sustainable and affordable product. The underlying assumptions are four-fold, that the coffee contents are of good quality, are safe when taken on a chronic basis, are effective on continued use, and are consistent on a day-to-day basis. These aspects are the fundamental principles of QSEC – quality, safety, efficacy, and consistency, which underpin the rationale for the dramatic paradigm shifts that are underway in traditional medicine today. Most of the world relies, to a greater or lesser extent, on plant materials for some form of their healthcare. All of these systems of medicines for patients (not consumers) are, like the coffee situation, based on the same fundamental assumption: that the plant or other organism necessary for the preparation of the medicine will be there when needed.

The study of the biological effects of natural resources, including traditional medicines, is known as “pharmacognosy”. In the 21st century, with burgeoning populations, increased life spans, and depleted natural resources, this definition, and the term itself, only meets one aspect of the requirements for a global healthcare science. However, before explaining the considerations for the future, some additional background is needed. The Preamble to the Constitution of the World Health Organization indicates that “the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, and political belief, economic or social condition”. Only when a population is healthy, and can be maintained that way, and not ravaged by disease, whether acute or chronic, that there can be reliable economic and social development linked to the effective and appropriate use of available resources. Planetary
health embraces this dynamic between the ecological health of the Earth and that of the organisms, including humans who are its interconnected biological inhabitants. The past 255 years, since the beginning of the industrial revolution in about 1760 in England, have seen the greatest increase in overall living standards, wealth, health maintenance, and economic, industrial, sociological, scientific, and technological achievement in human history.

However, that progress has occurred at a price which we are still learning to understand in terms of loss of biodiversity, warming of the Earth’s atmosphere, degradation of the environment, pollution, and the depletion of marine and terrestrial resources for food and other needs. Among the persistent requisites for health or for life-style maintenance are those depleted resources; clearly a paradigm must change.

One of the most famous American architects, Louis Sullivan, who was based in Chicago, in an essay in 1896 about the design of tall buildings, and while referring to “the sweeping eagle in his flight (and) the branching oak” wrote that “…form ever follows function. That is the law.” He applied his observations of nature to architectural design. In other words, know what the building is for, and then design the form of it to meet the requirements for the function. We will now apply the concept in the context of pharmacognosy by stating a purpose (function) and then designing the activities (form) to meet that purpose.

Discussion

So what then is pharmacognosy “for”? In the vast global picture of the medicinal, cosmeceutical, nutraceutical, agricultural, and other sciences, what is it supposed to do, and for whom? As a well-established, diverse, cutting-edge gathering of sciences and technologies, for what will it accept responsibility? After all, an architect accepts the responsibility to design and build a house, or a bridge, or a sports arena, and sometime later, there it is, the finished structure ready to use; the form following the function. For now, and this is only one aspect of pharmacognosy, let us focus on a role in health care and ask, what is the function of pharmacognosy in examining, delineating, and articulating, the niche for natural products in the future of global healthcare?

We are in the same situation that Alice was in when, 150 yrs ago, she first met the grinning Cheshire cat in Wonderland, 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”. The author, Charles Lutwidge Dodgson, a lecturer in mathematics and logic at Christ’s College Oxford for 25 yrs, and better known under his pseudonym, Lewis Carroll, was enunciating in 1865 what Sullivan was to codify 40 yrs later. For pharmacognosy, it remains a pertinent question. So where does pharmacognosy want to get to? What is its function? And is it prepared, in the global panoramic complexity of humanity today, and the possible very challenging scenarios of the future, willing to accept an assigned role? When a group of astronomers 45 yrs ago offered to explore the origins of the universe and its nebulae, galaxies, and other worlds, the Hubble telescope was born, and it lives on, 25 yrs after launching. As a result, we know more about the location of wondrous galaxies far, far into the universe than we do about the location on Earth of the medicinal plants essential for the traditional medicines required for healing the contemporary ailments of humanity. Until pharmacognosy decides where it wants to get to, it will forever be mired at the junction of status quo and societal responsibility. But we have digressed and deferred a critical issue: what is “ecopharmacognosy”?

To understand the need for the term, and therefore its definition, some further background is necessary.

What is Ecopharmacognosy?

Looking back, the word and its meaning were 25 yrs in development. Since 1987, the author has written about “pharmacognosy” from various perspectives, including its societal role, its importance for determining an evidence base for traditional medicine, and its use of cutting edge technologies. In 1993, a new, broad definition of “pharmacognosy” was enunciated, as alluded to earlier, as “the study of biologically active natural products”. In that definition, pharmacognosy is unlimited by the material source (plant, marine, microbial, insect, mammalian, etc.), or the research area (botanical, analytical, chemical, biosynthetic, biological, pharmacological, clinical, economic, legal, regulatory, etc.) In early 2012, following a report from a conference in London, it was realized that this term and this definition for pharmacognosy were inadequate for the contemporary challenges of the
field. The “State of the Planet Declaration” from the “Planet Under Pressure” Conference\textsuperscript{23}, called for a societal contract to encompass: i) global sustainability analyses based in science, ii) integrated, international, and solutions-oriented research, implemented and involving Government, society, scientists, and the private sector, and iii) enhanced dialog on issues of global sustainability. As a global science based fundamentally on the judicious use of natural resources, it was staggering to realize that pharmacognosy has barely begun to address these issues. The declaration was a powerful reminder that each of us, as citizens and scientists, has a role to play in terms of “sustainability”, and that it has to be a conscious and conspicuous component in our lives and in our work.

Every human health system, whether it is national, indigenous, tribal, or familial relies on the use of medicinal agents, which may be either synthetic in origin, partly synthetic and part natural (e.g. the steroid hormones), or totally natural, including single compounds, extracts, and plant and other materials used in traditional medicine. The fundamental assumption is two-fold, that the medicinal agent will be available, and that it will be accessible (i.e. both available and affordable). If the global population reaches 10 billion by 2040, just 25 yrs from now, how will accessibility to safe and effective medicinal agents, synthetic and natural, be maintained and expanded, and at what cost to patients globally\textsuperscript{17,19,22}? Confounding and compounding the complexity of the situation are three factors: i) the globalization (and therefore the unpredictable increased demand) for existing traditional medicine systems and products, ii) the development of new traditional medicine agents, phytotherapeutics, nutraceuticals, and cosmeceuticals, and iii) the vast “medicine cloud”, which includes the unregulated e-commerce of plant-based medicinal agents, which places further, completely unknown, and probably immeasurable demands on global medicinal plant resources. Together, these rapidly evolving markets are placing extreme pressures on the provision of authentic plant materials for commercial products. Few of these traditional medicines and phytotherapeutics are cultivated, they are dominantly (ca. 80% or more) wild-crafted, and as a result they are disappearing from local habitats, and in some cases appearing on lists of threatened species\textsuperscript{24,25}. In reality, the very resource being studied, the one that is essential for the primary health care of most of the world, is rapidly disappearing. Yet we are continuing to work on the assumption that the organism of interest will always be available, now, and in the future\textsuperscript{17,22}.

As the Mad Hatter exclaims to Alice, “We are all mad here”, for that notion of continued availability is clearly illusory\textsuperscript{19}.

About six years ago, the author began to discuss the concept of “sustainable medicines” in terms of both synthetic and natural medicinal agents\textsuperscript{2,12-15}. In retrospect, although it was progressive at the time in pharmacognosy, it was still “late-thinking”; for in the early 1990s the concept of “Green Chemistry” was launched\textsuperscript{26}, which, from a pharmacognosy perspective, could be offered as six practical principles\textsuperscript{13,21,27}. Have the global practices of pharmacognosy been examined and modified as a result of these “green” principles? Or has the notion of incorporating these principles been ignored, and we remain stuck at that crossroads again, fearful of taking the responsibility for the path less trodden? From a health care sustainability perspective, how much effort has there been globally to transform the utilization of plants in traditional medicine practices from a “forest economy” to a “field economy”\textsuperscript{24,28-30}?

“Ecopharmacognosy”, as a term, was introduced as a scientific meeting in Lublin, Poland in May, 2012. It is defined as “the study of sustainable, biologically active natural resources”\textsuperscript{21,19}. It is both a philosophical approach and a system of scientific practices based on that philosophy. It stresses the importance of environmental concerns in the field of natural product research from several directions; from the perspective of what types of materials should be studied, to opportunities for changing the practices used for their botanical, chemical, biological, and clinical study, to assuring a high quality, safe, effective and consistent (QSEC) product for the patient and the practitioner. An example will illustrate the concept. If a “function” of ecopharmacognosy is to develop new medicinal agents based on natural products, or to enhance the quality control of traditional medicines, then from a patient perspective, QSEC is essential. Within that scope there is accessibility, including, will the plant material always be available, as well as affordable. Thus, how to resource a plant material long-term on a sustainable basis is an early stage development question. Considering the development of a bark or root material is very different than the sustainable development of a leaf or fruit material. A reflection on the history of the development of paclitaxel from...
the bark of *Taxus brevifolia* Nutt. (Taxaceae) is illustrative in this regard. Ecopharmacognosy encourages the enhancement of green processes involved in the study of a plant for its active principles. It then evolves into a fundamental philosophical approach towards the conduct of natural product research in terms of resourcing, long-term environmental impact, processing, and the final product for the patient. As we shall see, it is also a practical aid in guiding how research priorities and research practices should be focused. To be societally relevant, pharmacognosy research must become more “eco-centric”. This is no longer a choice, it is a societal expectation. There are many areas, even within the healthcare system where cheaper, accessible medicinal agents are needed, needs which are not, and will not, be addressed by the major pharmaceutical companies, these include: population control, obesity, diabetes, diarrheal diseases, various tropical mosquito-borne and larval diseases, multidrug resistance, etc. Before giving some practical examples of ecopharmacognosy, however, let us turn to the quality control of traditional medicines.

**Traditional medicine quality control**

Once again, it is imperative that we begin with the perspective of the patient. Since each of us is a patient of some form of medicine, our individual and collective expectation is that when that medicine is acquired, we can be assured of its quality, safety, effectiveness, and consistency (QSEC) derived through a holistic approach. In addition, the products and practices of traditional medicine should be founded on the results of global information, evidence-based research, and sustainability, applied by trained and registered practitioners. This was the fundamental philosophy behind the Western Pacific Region Office Regional Strategy for Traditional Medicine 2011-2020, and also the WHO Traditional Medicine Strategy 2014-2023. In practical terms, what this means is that a transition is underway, moving traditional medicine practices and products from a knowledge-based system, to an experience-based system, and eventually to an evidence-based system. There are many aspects to this movement, including sociological, economic, professional training and registration of practitioners, patient education, diverse practitioner education, regulatory development, and as well as the scientific and technological integration in the era of “–omics”, etc. This paradigm shift will not be a rapid transition for the world to achieve……even though, as was mentioned earlier, the access to quality healthcare is a human right. It will require dedicated financial underpinning, an exceptional degree of inter-scientific collaboration and commitment, locally and regionally, and, as we shall see, intent.

Quality control, as the basis of traditional medicine content is also a major concern for ethical reasons. When a practitioner, allopathic doctor, shaman, curandero, hakim, medicine man or woman, “prescribes” a healing agent or modality, there is an expectation on behalf of both parties that the agent or modality will “work”, that it will be effective in either prevention or treatment. Who is responsible for assuring the control of that product, and who is responsible when it doesn’t work, or worse, causes harm? The government? The manufacturer? The practitioner? And what are the moral and ethical responsibilities of each party in this scenario to see that it does work? If the product is defective in some way, whose responsibility is it to know that? A recent case in the United States, placed a completely new “twist” on this conundrum, when the Attorney General of the State of New York decided to ban the sale of all health supplements in four large, national retailers (including Walmart and GNC) based on an investigation that the dietary supplement products being sold did not meet label specifications, and were therefore fraudulent. Previously, the focus of regulatory authorities was on the manufacturer of the product to assure product and label compliance, now the responsibility was being shifted. Could it next be shifted to practitioners who may be dispensing traditional medicines and phytotherapeuticals/dietary supplements? Either way, a system based on trust was shattered.

About 60 yrs ago, before the days of Sony, Canon, Panasonic, Toyota, Honda, and Toshiba as leading global Japanese brands respected for the quality of their products, an American management expert, W. Edwards Deming, went to Japan and brought a new era of focus on continuous quality improvement to Japanese industry. One of his aphorisms from that time is “Quality begins with intent”. Another is that “We have lived in a world…… of defective products. It is time to adopt a new philosophy”. From the perspective of traditional medicines and dietary supplements it incredibly remains the case that we are
still living in a time of defective products, and, as the New York case has shown, the industry professionals are still denying responsibility. That is our status quo and is absolutely not a very reassuring position for the patient. It is now time for a new philosophy, one which assures QSEC for the patient as an essential moral and ethical responsibility. Consequently, the development of standardized traditional medicines and dietary supplements, as well as the essential oils used in aromatherapy, is a fundamental scientific requirement, so that appropriate biological and clinical studies can be conducted for the benefit of the patient. The existing paradigm must completely change. A new path must now be trodden, globally. It must be patient before profit.

Myths of Traditional medicine

There are no illusions that such a deep paradigm shift will be easy; nothing profoundly worthwhile is. There are many, many barriers to overcome on the long pathway to QSEC. It is an unexplored trail, and as such will not be travelled in a few steps, and will not be travelled by scientists alone, for it will involve the integration of knowledge from multiple fields of study. However, the journey must now begin in earnest……for the future health and safety of the patient, and for the ethical assurances of the practitioner. One of the very first barriers encountered to the development of enhanced traditional medicine quality control is to recognize that the social and economic systems, as presently constructed and portrayed, are built on a series of myths. A myth is defined as: “an unproved or false collective belief that is used to justify a social institution” (www.dictionary.com). Myths are frequently of fundamental importance in supporting the structures of societies, and the global “society” of traditional medicine is no exception. The holders and purveyors of the myths, in the case of traditional medicine those with the accumulated folk knowledge, as healers, frequently held (and do hold) great power in their respective society. Thus it was, and remains today, in their interest to maintain these myths. There are thirteen myths associated with traditional medicines, and an important one regarding traditional medicines associated with allopathic medicine, only a brief summary will be offered here.

The thirteen global traditional medicine myths are:

i) this traditional medicine has been used for thousands of years, ergo it is safe and effective;

ii) using the “correct” plant is adequate; iii) the biological effects are the same from different plant parts; iv) the biological effects are the same irrespective of the geographic origin of the plant; v) the biological effects are the same irrespective of the method of plant preparation; vi) older plant material is less effective (or possibly more toxic); vii) “wild”-collected plants are more active than cultivated plants; viii) all of the materials in a complex prescription are necessary for effectiveness; ix) complex mixtures of plants cannot be standardized; x) this medicinal plant product is already well-regulated; xi) medicinal plants are safer than synthetic drugs; xii) the medicinal plant will always be available; and xiii) the traditional knowledge will always be there. The fourteenth myth, operating from the modern medicine system perspective, is that “traditional medicines are not effective, and are therefore not worth considering as a part of a contemporary healthcare system”. This myth, namely that plants are not powerful enough to heal, indeed are innocuous, is a fundamental and unjustified lack of respect for alternative healthcare systems, and a substantial barrier to effective patient care. After all, for the patient, there is only a medicine, the source is of no consequence; like the coffee, “it just has to work”. All of these myths must be “busted”, that is, explored through the application of respective scientific investigations, if the exploration of the important information that traditional medicine knowledge offers contemporary health needs is to become evidence-based for optimum patient benefit.

Developing Standards for Traditional medicines

With the notable exception of the United States, many countries and economic blocs in the world, including emerging nations, are evolving standards for the quality control of traditional medicines and phytotherapeutics as their healthcare systems become more integrated and holistic. At the same time, a number of these countries are also seeking to globalize selected traditional medicines. The pitfalls in such an approach are numerous, in part because the standards for sale in a given country, or in a given region, are highly variable. The advice for standardization is therefore to aim high, regionalize and harmonize standards, and develop a cost-effective way to do it. Only assuring the patient that the correct plant is in a capsule or sachet, based on historical
precedent, and that there are no unproven medical claims on the label, is thinking from over 20 yrs ago; the world is moving on from that place. In a world where the quality (QSEC) of a traditional medicine is a prime intention, and that the quality is evidence-based from a patient perspective, leads to some basic parameters for a product. These parameters include the development of information systems which capture and compare traditional knowledge on a global basis (taking into account the intellectual property rights issues), and accumulate the scientific knowledge about those plant materials. They also include the development of standards that are based on plant DNA barcoding for authentication, as presented in the Chinese Pharmacopoieia, standards for the identification and analysis of the biologically active principles, and analytical procedures that will eliminate contamination by adulterants, pesticides, heavy metals, microbes, etc. The parameters must include studies that will, at least initially minimally, assure that available commercial preparations are safe and effective, and can be presented consistently, through the evaluation of standardized preparations in vitro, in vivo, and in humans. In this process, there is an opportunity to investigate the philosophies in traditional medicine systems of multiple component plant preparations through network pharmacology. Finally, there is the application of Good Agricultural and Collection Practices, Good Laboratory Practices, Good Manufacturing Practices and Good Clinical Practices in developing a particular product. Ecopharmacognosy has both a philosophical and a practical role to play in each of these areas, and some examples, mostly from our collaborative studies, will be presented briefly.

The experience that most people have with chili peppers is illustrative of what can be expected when the biological activity of a plant used as a traditional medicine is considered. The hotness of the peppers of Capsicum annuum L. (Solanaceae) is measured in Scoville Heat Units, a rating process originally devised in 1912 by the American pharmacist Wilbur Scoville. The range of “hotness” for peppers can be from 0 to ca. 1.6 million based on the capsaicinoid content. Although this method, from a regulatory perspective, is replaced by various HPLC methods, some of which can separate all of the relevant capsaicinoids, the underlying feature is that of high variability of the biologically active principles (a characteristic taste sensation in this instance).

Clearly, the same variability must be expected, assessed and standardized for the active principles of all traditional medicines for the expectations of the patient to be fulfilled. This raises another issue, namely, “What is the dose of a traditional medicine?”, and how is that established? Is a scale of effectiveness needed for a traditional medicine so that the dose for the patient can be assured on a batch to batch basis? Or is it “Western thinking” that the identification of a particular “dose” is required for healing? Only the application of time and well-planned science will assist in resolving those basic questions for the patient.

Recently, a holistic approach to the quality control of traditional Chinese medicines was described. The method involves plant authentication, several types of analytical chemical information coming from single compounds, extracted fractions and whole plant sample, coupled with a multi-level biological system which integrates information from pharmacology, molecular biology and systems biology. The goal of the approach is to establish a simple, cost effective, QSEC framework based on one or two key components in a plant, which can serve as a pharmacopoeial standard.

Practical aspects of Ecopharmacognosy

A fundamental aspect of ecopharmacognosy is to be conscious that natural materials are being used optimally, and not to waste precious plant and human resources to develop and promote the sale of ineffective products. Knowing the constituents and how they relate to a biological response, and which constituents are important, and how they potentiate or antagonize the effects of multicomponent matrices, are core aspects ecopharmacognosy in traditional medicine development with respect to QSEC. The metabolome of a single plant can be extremely complex. Even the exceptionally well-studied Panax ginseng C.A. Mey., Panax notoginseng (Burkill) F.H. Chen ex C.H. Chow, and Panax quinquefolius L. (American ginseng), all in the Araliaceae), recently revealed the presence of 623 ginsenosides between the three plants, of which 437 were probably new. However, this detailed analysis allowed the development of simple, unequivocal and specific biomarkers for each plant, an important aspect in optimizing the commercial quality control of the respective plants, and examining for fraudulent products. As another example of metabolomics, the
effect of five different, currently used, processing techniques on the chemistry of Kansui radix, the roots of Euphorbia kansui T.N. Liou ex S.B. Ho (Euphorbiaceae), was examined by proton NMR spectroscopy. The result was that five, quite different, chemical compositions were observed. From the patient perspective, which is the one that is the safest and has the best clinical efficacy (if any)? Other studies have examined whether the composition of the same, multiple plant mixture from different companies in different parts of China reflects the same breadth and depth of chemical composition; they did not. Determining which of these preparations is the most effective will establish from where the relevant plant materials should be obtained and how they should be prepared, thereby potentiating production of the most effective plant as a crop.

Four other examples of the practical influence of ecopharmacognosy will be presented. The secondary metabolic biosynthetic genes of plants are poorly known at this point. However, some inferences can be gleaned from the biogenetic pathways and the functional groups which are displayed in the products isolated. Enzymes derived from fungal sources are available to conduct a number of commercially important chemical transformations. However, omitting the enzyme isolation step, more recently, the use of readily available, whole plants as chemical reagents has also begun to be studied, with significant success, in that reduction and acylation reactions can be achieved in high yield, under very mild conditions. Furthermore, reductions of ketone groups to produce a chiral alcohol proceed with a very high degree of enantioselectivity, with a 6-7-fold reusable catalyst, using a variety of common vegetables. These reactions are significantly more cost effective to conduct, and have a markedly reduced ecological impact in the absence of expensive, single use, non-recyclable, heavy metal, or chiral hydride reducing reagents. This is clearly an area of tremendous potential development in the future as the basic resources for allopathic drug synthesis become more expensive, and the medicinal agents more costly for the patient.

The anti-obesity effects of caraway seed aqueous extract were recently evaluated in a clinical trial, together with the safety of the preparation. Many plant materials have been proposed as assisting in overcoming the global phenomenon of weight gain and the health complications that can arise as a result. Caraway seed was chosen to evaluate for a number of reasons, including traditional use, and also because it is already a commercial product, and therefore sustainable sourcing of the required material for commercial development would be assured.

Significant effort and resources are wasted in bringing plant materials from the field to the laboratory for chemical and biological analysis for drug discovery purposes, or when samples are harvested for traditional medicine purposes. Either way, the content of the bioactive metabolites at the time of harvesting is not known until much later, and from a patient perspective, not optimized. One way to overcome some of these issues is the “pharmacognosy in a suitcase” approach, where the laboratory, in some form, which may include lab-on-a-chip or remote sensing devices or hyperspectral imaging, can be used on small plant samples in the field. This takes advantage of accessing a minimum amount of plant material with maximum impact. Such techniques are already widely used in the cultivation of wine grapes, as well as other agricultural crops, and for the detection of plant diseases. Pestle and colleagues have recently used non-invasive technologies to quantitate the collagen (a polypeptide) content in archaeological bone samples.

**Importance of Network Pharmacology**

Potentially, one of the most important contemporary aspects for the future of ecopharmacognosy in the use of plants in traditional medicine is “network pharmacology”, a term introduced by Hopkins in 2007 based on studies of how a single drug resulted in a plethora of biological responses. The old thinking, dominant in the drug discovery arena in pharmaceutical companies for decades, was the “magic bullet” approach, “one target, one drug”. Now, the philosophy has shifted to “network target, multiple components”. It postulates that a network target can be defined at the genome level, and therefore provide a way to define the mechanistic impact of medicinal agents, allowing examination of the overlap with other disease or response networks. Given that a traditional medicine is a vastly complex, multicomponent, metabolic matrix, one might expect that this will have a major impact on understanding how traditional medicines act at the genome level, once genome maps of adequate numbers of natural products occurring in the
traditional medicine plants have been developed into databases for analysis.\(^{51,52}\)

A number of important applications of network pharmacology are already apparent, and more will surely follow, including: i) discerning both the active ingredients and their biological role in complex plant matrices; ii) observing synergism... when the observed biological response is greater than predicted due to multiple nodal interactions; iii) examining the holistic theories which undergird the use of complex plant mixtures; iv) explaining and possibly predicting, the toxicities or potential adverse reactions of specific plant combinations; and v) postulating new biological activities of known compounds, and/or new combinations of medicinal plants with unforeseen medicinal uses.\(^{51}\)

From an ecopharmacognosy perspective, it is envisioned that the approach will allow for a more judicious selection to be made of the plant materials required for a complex prescription, thus preserving the use of some plants for other remedies, as well as rationalizing why certain plants are viewed as essential in a multi-plant mixture.

**A Way Forward**

With this abbreviated background, and recalling the earlier discussion, some directions for the way forward for studies in ecopharmacognosy, within a sustainability and more eco-conscious construct, should include the following. Envisioning the development of traditional medicines, including their quality, safety, efficacy, and consistency, as a wider societal responsibility to integrated healthcare. Developing mechanisms for cooperation and collaboration between relevant sectors of the government, academia, and the manufacturing industry for a long-term, staged program of the development of people, information systems, and facilities, focused on improving traditional medicines for the benefit of the patient. Developing focused, highly collaborative and interactive research groups at centers of excellence which can explore traditional medicines, by establishing decision-making protocols for prioritized traditional medicine scientific investigation based on a countries healthcare needs and societal priorities. Considering the ethical issues of waiting for an evidence base vs. existing scientific evidence in recommending the marketing of specific preparations for patient use (risk vs. benefit). In examining the biological effects of plants \textit{in vitro}, \textit{in vivo}, and in humans, testing only well-standardized and consistent traditional medicine materials, so that the results are reproducible. Developing quality clinical trials that are relevant to the projected use(s), and fully report both positive and negative results. Establishing networks for required pharmacovigilance for the interactions between traditional medicines, and between allopathic and traditional medicines. Enhancing practitioner education and communication within and between the different systems of medicine in order to engender respect on both sides of what each set of clinical experiences has to offer in an integrated healthcare system. Conducting conservation and agronomic studies to assure that accessibility to traditional medicines is maintained.

In these ways, ecopharmacognosy will stay relevant, have multiple functions, and be able to formulate long term plans for engagement toward a healthier society in which the needs of the patient are the highest priority.

**Conclusion**

Ecopharmacognosy, as a philosophy and practice, brings and includes, the critically important concept of sustainability to the study of biologically active natural products. It seeks to encourage the consideration of sustainable development of natural products in healthcare, cosmeceuticals, nutraceuticals, and agriculture at an early stage in the development process. In addition, it posits that the use of non-sustainable plant parts and of wild-crafted plant and other biological materials in traditional medicine should be minimized, in part through the application of integrated and diverse natural product sciences. It seeks to promote the processing of plants under conditions which require lower energy consumption and reusable supplies, and encourages the development of alternative strategies for organic synthesis involving common plants and vegetables. It also supports the \textit{in silico} evaluation of known compounds as enzyme inhibitors prior to \textit{in vitro} testing to conserve resources and valuable metabolites. Finally, ecopharmacognosy offers a pathway for rethinking how pharmacognosy can contribute to the global call for sustainable thinking and practices.

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