Ethnobotany, phylogeny, and “omics” for health and food

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Abstract

Here, we propose a new term, 'ethnobotanical convergence', to refer to the similar uses for plants included in the same node of a phylogeny. This phylogenetic approach, together with the 'omics[20TD$DIF]' revolution, shows how combining modern technologies with traditional ethnobotanical knowledge could be used to identify potential new applications of plants.

Ethnobotany and the search for new drugs and foods: the classical approach

Plants have always been a crucial resource for humans. Ethnobotany is the discipline, located in the interface of natural and social sciences, addressing the relationships between human groups and plants. Amongst all plant applications, those related to human health and wellness are the most diversified and extended. Bioprospecting for new drugs of plant origin and for new food crops has classically been based on ethnobotanical information. Ethnobotanically-directed bioprospecting has importantly become more powerful than random assays for finding and identifying bioactive compounds from plants. Aspirin (from *Filipendula ulmaria* (L.) Maxim.), codeine and papaverine (from *Papaver somniferum* L.), colchicine (from *Colchicum autumnale* L.), digoxin and digitoxin (from *Digitalis purpurea* L.), tetrahydrocannabinol and cannabidiol (from *Cannabis sativa* L.), and vinblastine and vincristine (from *Catharanthus roseus* (L.) G.Don) are amongst the most famous classical drugs developed from ethnobotanical leads [1]. The first evidence of the anticancer properties of paclitaxel, from *Taxus* L. species, was its toxic effect on murine leukaemia cells, in agreement with the popular knowledge of the general toxicity of these plants. The success of this anticancer product provides an indication of the promising role of plant products in drug development. Oseltamivir was more recently developed (from *Illicium verum* Hook.f.) during the epidemic of avian flu based on ethnobotanical data from Chinese traditional medicine. Ethnobotanical records also led to the isolation and development of artemisinin (from *Artemisia annua* L.) as a powerful antimalarial drug [2], whose relevance was recognised with the 2015 Nobel Prize in Physiology or Medicine.

The new approach: linking ethnobotanical convergence, phytochemistry, and molecular phylogeny to predict plant uses

New perspectives have opened with the emergence of new molecular tools, especially for DNA sequencing, allowing phylogenetic reconstruction with hot nodes clustering potentially useful plants, including species traditionally used for medicinal purposes (Fig. 1). Promising predictions of medicinal plant uses have been developed based on the conjunction of ethnobotanical, phytochemical, and molecular phylogenetic data [3].

The use of the same (or closely related) species in the same ways in different cultures indicates that different and often non-interacting human groups have independently acquired this knowledge, because some plants have similar morphological characteristics from a shared phylogeny, a phenomenon termed evolutionary convergence. In this case, we propose to speak of plant-use convergence or ethnobotanical convergence for the similar uses for plants included in one node of a phylogeny.

Determining the phylogenetic relationships amongst plant species could be an appropriate tool for discovering new drugs based on recorded plant medicinal uses and analysing ethnobotanical data. Plants evolving in the same lineage have more medicinal uses than evolutionarily isolated species, and the diversity of medicinal uses is correlated with the evolutionary history of the species. Species-rich clades are more likely than species-poor clades to contain taxa with more uses, and ancient taxa are less abundant in the flora, so less used in traditional medicine [4].

For instance, *Pterocarpus* Jacq. species used to treat certain illnesses were significantly clustered in the phylogenies, since related plants had the same medicinal uses in parallel in very distant areas: the Neotropics, tropical Africa, and Indomalaya [5]. This excellent example of ethnobotanical convergence illustrates the ability of different cultures to discover related plants to treat similar disorders.

Another clear example of ethnobotanical convergence is provided by the spices used as condiments for two products in different geographical and cultural areas. Pizza in Western cultures is seasoned with *Origanum vulgare* L., and Near Eastern similar food (*manousheh*, in plural *manaqish*) uses another species of the same genus as condiment, *O. syriacum* L. Both taxa are phylogenetically very close, implying a similar chemical composition and so a similar use.

Chemical properties are evolutionarily conserved [3], so bioscreening could be targeted to the lineages identified as hot nodes for medicinal properties. As a result of evolution, widely distributed species could synthesise metabolites to adapt to their ecological amplitude more than species of restricted distribution and with a local evolutionary history, perhaps explaining why only 62 of the 457 families of angiosperms and gymnosperms are used as sources for medicinal drugs [6]. Nevertheless, the relationship between one specific active principle and a medicinal activity is not always clear, complicating the phylogenetic prediction of plant uses.

Combining omic techniques with ethnobotanical approaches

In addition to the phylogenetic approach, the large data sets obtained using omic techniques (e.g. genomics, transcriptomics, proteomics, and metabolomics) and their analyses with bioinformatic tools are becoming very useful to identify the best plant taxa (or genes within these taxa) for medicinal and alimentary uses amongst plants with popular ethnobotanical uses. DNA barcoding should be used for species identification in conjunction with chemical analyses to detect and quantify the required chemical compounds. These methods and the resulting data sets also provide a better understanding of the evolutionary history of medicinal and alimentary plants. An exhaustive review of the evolution of chloroplast, mitochondrial, and nuclear genomes in several medicinal, edible and ornamental plants is provided in [7].

The rapid development of the main techniques used in the analyses of metabolites, e.g. gas chromatography, high-performance liquid chromatography, and nuclear magnetic resonance, is also rapidly increasing the application of metabolomics in many aspects of natural-drug (and food) discoveries (Fig. 2). Metabolomics, the technology designed to provide general qualitative and quantitative profiles of metabolites in organisms exposed to different conditions, allows monitoring the spatial and temporal distribution of target phytochemicals influenced by plant developmental and environmental cues [8]. Metabolomics also identifies compounds related to a target phytochemical, which may be considered as either intermediates of biosynthesis or useful alternative products of promiscuous enzymes that support the biosynthesis of the target phytochemical. Metabolomics also promises a better understanding of the effects of complex mixtures, such as those used in traditional Chinese medicine. In fact, assigning bioactive compounds from complex mixtures is a central challenge of natural-product research. The combination of bioassay-guided fractionation with untargeted metabolite profiling improves the identification of active components [9]. Metabolomics is also enabling a better understanding of medicinal plants and the identification of important metabolic quantitative trait loci for enhanced breeding. This metabolomic approach may have the potential to greatly advance natural-product research and development of scientifically based herbal medicine, changing the paradigm in medicinal bioprospecting [10], thus becoming an excellent complement for the development of new wellness products from popular ethnobotanical uses, for both medicine and food.

The integration of this metabolomic approach with genome-based functional characterisations of gene products from ethnobotanically important plants is providing an accelerated path to discovering novel biosynthetic pathways of specialised bioactive metabolites. This integration has thus strongly enhanced the potential discovery and production of pharmaceutical and alimentary products. For example, the production of the famous anti-malarial drug artemisinin is being enhanced via traditional breeding, with new high-yielding hybrids to convert *Artemisia annua* into a robust cropping system, and by the reconstitution of the artemisinin biosynthetic pathway in a re-engineered microbial host [11]. Another example of a successful integration of omic techniques with ethnobotanical approaches is the discovery of a series of FAD2 phytochemicals in a non-plant bioengineered host system after comparison of the transcriptomes and metabolomes of developing seeds that accumulate unusual fatty acids [12].

Genomics, proteomics, and metabolomics are high-throughput technologies that may economize the determination of the mode of action of phytomedicines and allow the investigation of herbal extracts without prominent active principles. The application of the omic technologies may thus lead to a change of paradigm towards the utilization of complex mixtures in medicine and nutrition. Metabolomics and other omic techniques have generally thus proven very valuable, but they still face substantial challenges, including large-scale metabolite identification. The further development of the field of metabolomics in particular and omics in general, however, will continue to provide better tools for the discovery of the next generation of natural products inspired by popular knowledge gathered in ethnobotanical studies and enhanced by recent phylogenetic approaches.

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Figure captions

Figure 1. Examples of Medicinal or Food Plants Used in Various Locations around the World. Chemical products (medicinal use given in brackets) and DNA sequence-based phylogenies involved in the molecular phylogenetic prediction of plant activities are shown.

Figure 2. Natural Product Discovery. Merging ‘omic’ techniques with a traditional workflow for the discovery of natural products in plants based on ethnobotanical and phylogenetic prospecting.

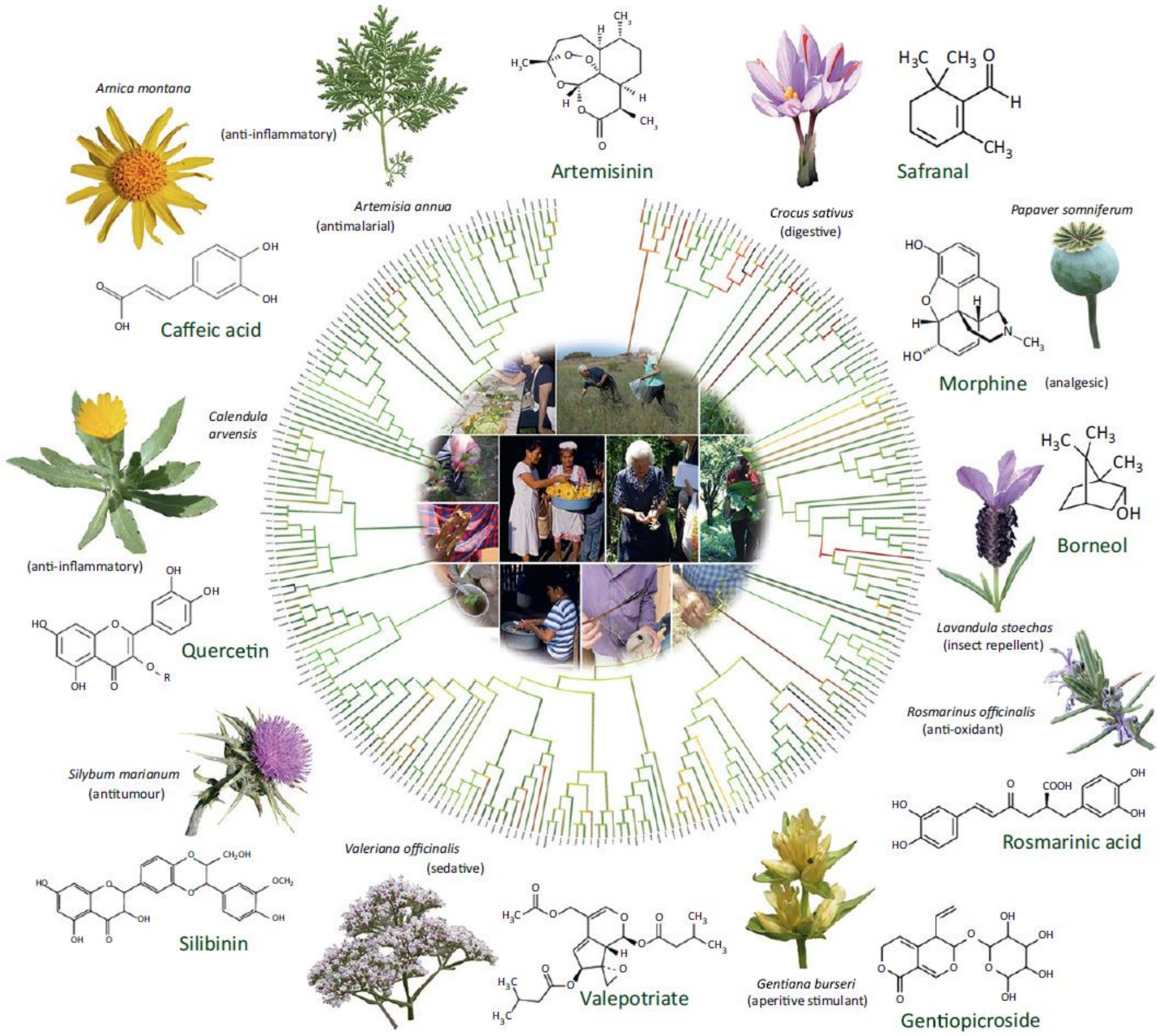

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Figure 1

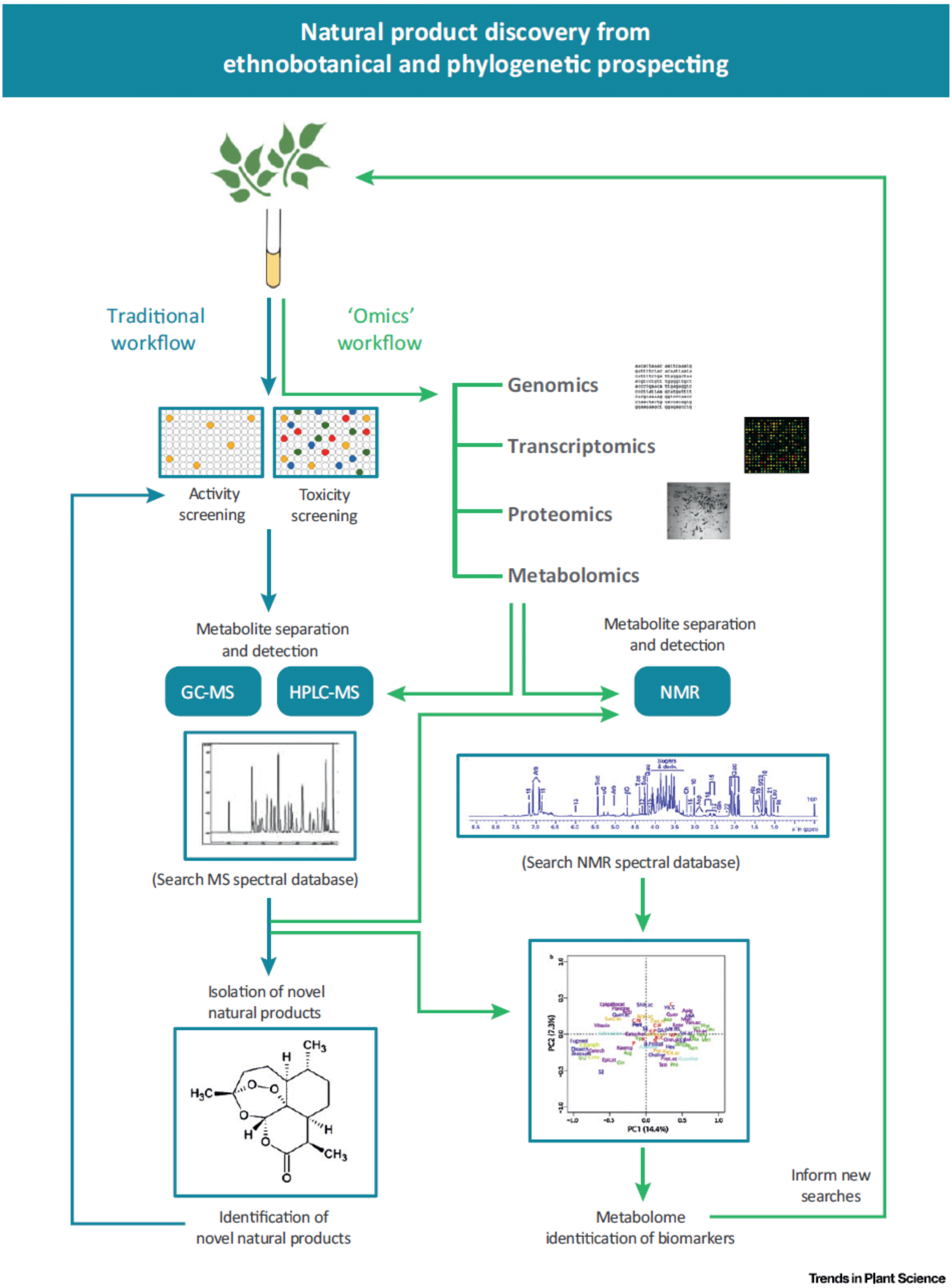
Natural product discovery from ethnobotanical and phylogenetic prospecting
Traditional workflow
'Omics' workflow
Genomics
Transcriptomics
Proteomics
Metabolomics
Activity screening
Toxicity screening
Metabolite separation and detection
GC-MS
HPLC-MS
Metabolite separation and detection
NMR
(Search MS spectral database)
(Search NMR spectral database)
Isolation of novel natural products
H_3C
H
CH_3
O
O
O
H
H
O
CH_3
O
PC1 (14.4%)
PC2 (7.3%)
Identification of novel natural products
Metabolome identitication of biomarkers
Inform new searches
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Figure 2