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Review

Medicinal plants meet modern biodiversity science

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SUMMARY

Plants have been an essential source of human medicine for millennia. In this review, we argue that a holistic, interdisciplinary approach to the study of medicinal plants that combines methods and insights from three key disciplines — evolutionary ecology, molecular biology/biochemistry, and ethnopharmacology — is poised to facilitate new breakthroughs in science, including pharmacological discoveries and rapid advancements in human health and well-being. Such interdisciplinary research leverages data and methods spanning space, time, and species associated with medicinal plant species evolution, ecology, genomics, and metabolomic trait diversity, all of which build heavily on traditional Indigenous knowledge. Such an interdisciplinary approach contrasts sharply with most well-funded and successful medicinal plant research during the last half-century, which, despite notable advancements, has greatly oversimplified the dynamic relationships between plants and humans, kept hidden the larger human narratives about these relationships, and overlooked potentially important research and discoveries into life-saving medicines. We suggest that medicinal plants and people should be viewed as partners whose relationship involves a complicated and poorly explored set of (socio-)ecological interactions including not only domestication but also commensalisms and mutualisms. In short, medicinal plant species are not just chemical factories for extraction and exploitation. Rather, they may be symbiotic partners that have shaped modern societies, improved human health, and extended human lifespans.

Introduction

Medicinal plants are used to maintain physical, mental, and spiritual health in all cultures and in a variety of capacities and contexts. Such plants include species with one or more organs that produce compounds of clinically established therapeutic value, which may be utilized directly or as precursors for drug synthesis, and others that have not been vetted as such but are believed to be therapeutically useful (e.g., as medicine, tonic, food, or cultural symbol)[1–3]. Iconic examples include: *Papaver somniferum* L. (opium poppy), from which are derived powerful pain-relieving alkaloids like codeine and morphine; *Cinchona ledgeriana* Wedd. (fever bark) and *Artemisia annua* L. (wormwood), which yield lifesaving antimalarials; *Catharanthus roseus* L. (G. Don) (rosy periwinkle) and *Taxus brevifolia* Nutt. (Pacific yew), from which anticancer treatments like vinblastine/vincristine and paclitaxel, respectively, have been synthesized; and *Dioscorea mexicana* Scheidw. (Mexican yam), the source of diosgenin, a potent steroid for oral contraceptives[4–6]. As these remedies were discovered, humans greatly facilitated the migration of these medicinal plant species and sought to enhance their diversity. The breadth of such interactions and the numerous benefits that plants provide to humans illustrate why improved knowledge and conservation of medicinal plant species are essential[7,8].

Humans have used medicinal plants since at least 2600 BCE[9,10] and perhaps for upwards of 30,000 years[11]. Moreover, for hundreds of thousands (to millions) of years, paleolithic hominins likely used many plants to cure diseases or at least to ameliorate their symptoms[12,13]. Today, an estimated 80% of people worldwide use traditional herbal medicines[14–18]; they are the first line of defense against disease for tens of millions of people. Despite the ubiquity and longstanding cultural significance of medicinal plants — totaling at least 30,000 species[19] — traditional uses of most medicinal taxa have not been evaluated clinically[9]. In parallel, only 16% of plants thought to have therapeutic value have been tested for biological activity[20].

Most contemporary research on medicinal plants is rooted in early- to mid-20th-century efforts that focused on the biochemical characterization, pharmacological activity, and synthesis of phytomolecules with potential medicinal utility[21]. In the United States alone, ≈9% of approved drugs are derived directly from plants; this figure is nearly three times higher globally[22,23]. Moreover, many drugs in widespread use are synthetic analogs of plant secondary metabolites (e.g., aspirin, codeine, morphine)[24]. Although many tangible leads continue to be derived from natural products[25,26], the pharmacological industry predominantly uses libraries of synthetic compounds for screening purposes. However, of the 1073 new compounds that were approved for pharmaceutical use from 1981 to 2010, only 36% were purely synthetic whereas >50% were derived or inspired by nature, mostly from plants[22,27]. Concomitantly, exploration of plants as direct sources of medicines has declined precipitously[22,26] because of the perceived high cost/benefit ratio of field exploration, complications with alpha taxonomy, low tissue yields, slow growth, varying harvesting and extraction protocols, and barriers to shared exploration raised by protectionist

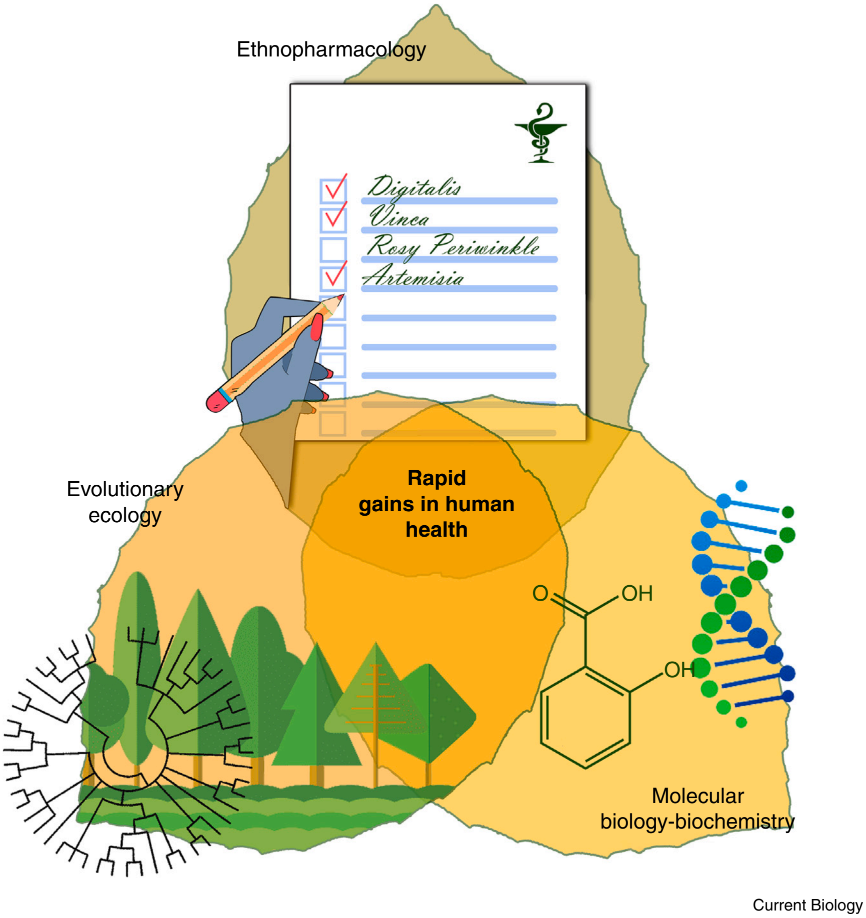

Figure 1. A framework for an emerging biodiversity science of medicinal plants.
The combined insights from three interconnected disciplines of modern biodiversity science could lead to rapid improvements in human health and well-being.

laws pertaining to the Nagoya Protocol[26,28,29] (officially named the "Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity". An addendum to the 1992 UN Convention on Biodiversity, the Nagoya Protocol was adopted on 29 October 2010 in Nagoya, Japan and entered into force on 12 October 2014. As of April 2023, it has been ratified by 139 countries (https://www.cbd.int/abs/nagoya-protocol/signatories/, Accessed 15 April 2023)). Although we recognize that drug discovery through synthesis has yielded significant gains in targeted pharmaceutical activity, this narrow focus of research has largely ignored the richer historical context of interactions between plants and people.

In this review, we suggest that interlinked research efforts in three major disciplines — evolutionary ecology, molecular biology and biochemistry, and ethnopharmacology — are poised to revolutionize the exploration and use of medicinal plants (Figure 1). The challenges in creating pharmaceuticals from single active compounds are being overcome by integrating evolutionary and historical perspectives on traditional herbal medicines shaped by millennia of human trial and error, and linking these perspectives with novel biotechnological and ethnobotanical applications[30,31]. These perspectives are opening the door to the reinterpretation of medicinal plants through a modern scientific lens. To help spark this revolution, we synthesize recent scholarship from these three disciplines that leverages data and methods spanning space, time, and species, and that are related to medicinal plant evolution, ecology, genomics, and metabolomic trait diversity. This research is usually siloed within one of these disciplines, but a more synthetic, integrative approach is beginning to emerge — one that builds strong intellectual bridges between these disciplines — that will help to elucidate patterns and processes that have given rise to medicinal plants and their relationships with humans, and lead to rapid advancement in the discovery and development of therapeutic medicines.

Evolutionary ecology

Evolutionary ecology seeks to understand the origin of species and their evolutionary relationships, establish how interspecific interactions are influenced by biotic and abiotic environments, and determine how selection and adaptation have influenced spatiotemporal changes in the distribution, abundance, and traits of species[32]. Modern theories and concepts from evolutionary ecology rarely are included in medical school curricula[33–38], despite focused efforts to incorporate these themes more centrally[39,40]. Evolutionary ecology is applied uncommonly to the discovery and identification of medicinal plants, and even less frequently to incorporating assessments of their evolutionary relatedness and interactions with the environment, humans, or other organisms, or for developing a better understanding of their most useful traits. However, new efforts are emerging that seek to link ethnopharmacology (see also the section on Ethnopharmacology, below) and human culture with ecologically-oriented research questions to address relationships between humans and plants[41]. For example, hypothesized centers of medicinal plant origins include disturbed habitats near human settlements where plants (often considered to be 'weeds') have been demonstrated to represent significantly elevated sources of raw materials for development as medicines[42].

New directions in discovering and identifying medicinal plant species

Advances in evolutionary ecology are improving our ability to discover and identify medicinal plant species along three fronts: online mobilization of biodiversity data, DNA barcoding, and more rigorous delimitation of species boundaries.

Mobilizing biodiversity data online via digitization from herbaria, field observations, and published literature speeds discovery[43–45]. Ambitious efforts by biologists and computer scientists to use these data to automate species identification and plant phenotyping from digitized content are well underway and yielding promising results[46,47].

DNA barcoding can identify specimens that are sterile, from juvenile plants, poor in quality, or from material that exists only as a pill or medicinal concoction. It also liberates taxonomic knowledge that can be used readily by scientists worldwide. DNA barcode libraries have been produced for species representing important medicinal plant families[48–50] (Figure 2A) and from biodiverse regions[51]. However, the vast majority of medicinal plant species have not been included in large-scale barcoding initiatives or broadly aggregated and mobilized in an accessible, community-friendly format[51]. Moreover, the short barcodes used to identify these species are not universal and often fail to accurately discriminate between close relatives[52], an important feature for identifying target species and close relatives of known medicinal value (e.g., *Artemisia* ssp.[53]) or for identifying adulterants or closely related non-target relatives that can be dangerous if mistakenly administered (e.g., *Actaea racemosa*, black cohosh[54]). Conventional barcode methods are not universal, lack resolving power, and often do not use whole genome sequence data, which are more easily incorporated into machine-learning approaches for rapid and accurate species identification as implemented in *varKoder*, a universal barcoding method for the Tree of Life[55]. Metabolomic analysis represents an alternative to DNA barcoding, and has power for finely discriminating important infra- and interspecific biochemical variation, but may be less reliable for species identification because the chemical composition of plants can vary widely with, for example, geography, climate, plant age, plant part, storage, and processing[50,51].

Biodiversity data, barcoding, and other methods for identifying genetic diversity are leading to clearer delimitation of medicinal plant species[56]. For example, the genetic diversity of Liang Mian Zhen (两面针; *Zanthoxylum nitidum* (Roxb.) DC.), used to treat rheumatism and other diseases, suggests that it actually is a complex of four distinct species rather than one[56]. In contrast, five taxonomically recognized species of *Corydalis* cultivated mainly in China and used for pain relief and blood circulation throughout East Asia for centuries were synonymized based on targeted molecular investigation[57]. More than 80 alkaloids have been isolated and identified from one *Corydalis* species alone (*Corydalis yanhusuo* W. T. Wang), revealing the potential for further drug development once the individual species are delimited more clearly[58]. Similar genetic investigations are needed to reconcile associated genetic clusters with taxonomy, especially using coalescent models[59]; to help develop more effective barcodes[55]; and to associate distinct genetic clusters with populations of plants with varying phytochemical profiles and uses.

Phylogenomic applications to elucidate the origin and utility of medicinal plants

Next-generation sequencing technologies combined with phylogenomic investigations are crucial for elucidating the origins of medicinal plants and their spread by humans, pinpointing evolutionary 'hot zones' of clades that include a high proportion of medicinal plants, and identifying their close (wild) relatives[60]. These approaches collectively will help us understand better where and in what context people began to use medicinal plants, how these plants have evolved, and whether their use in traditional and modern pharmacopeias has persisted.

Phylogenomics can resolve where and how many times medicinal plants have evolved in particular lineages; *Erythroxylum coca* (coca) in South America (Figure 2B) and *Cannabis sativa* L. in China[61,62] are recent examples. Ancient DNA (aDNA) also is being applied to explore the history of medicinal plant usage[63]. Herbaria and anthropological collections are important sources of aDNA[43] that could illuminate further the chronology of key genetic changes in medicinal plant lineages, including artificial selection for genotypic and phenotypic traits of medicinal use. Indeed, selection contributing to domestication may be detectable at the genetic level and may arise before the onset of readily discernible morphological variation[64]. Such investigations can be complemented by radiocarbon dating of archaeobotanical plant remains[11,65,66], some of which may include direct assessments of ingestion by humans[11,66,67].

Phylogenomic approaches also offer predictive and explanatory potential to explore plant species for therapeutic molecules. These approaches already have identified closely related plants representing phylogenetic hot zones spanning continents, climates, and cultures[60] (Figure 2C). At least 11 major plant clades provide significant compounds for use as, or derivation of, approved drugs[9,68], including antimalarials[69,70], antimicrobials[71–73], and molecules for treating cardiovascular disorders[74]. Such efforts could be enhanced further when guided by traditional or Indigenous knowledge[60,75,76]. Moreover, recent chemotaxonomic work has confirmed the existence of medicinal hotspot clades, and also has demonstrated that medicinal plants are not readily distinguishable from their congeners based on secondary metabolite profiles, pointing to potentially as-yet unexplored reserves of therapeutic species[77]. The significant clustering of medicinal plant species demonstrates that phylogenomic and chemotaxonomic approaches, combined with traditional medicinal knowledge from ethnopharmacology, can enrich our understanding and conservation of medicinal plants (see also Ethnopharmacology section, below).

Interactions between medicinal plants and their environments

Delimiting the geographic ranges of medicinal plant species is essential for identifying how their distributions interact with climate[78] (Figure 2D). Yet, the aggregated biodiversity data required for delimiting the geographic ranges of these species are, at best, widely dispersed. Consequently, it remains difficult to find and study medicinal plant species in the wild, assess their ecological correlates and model their current distributions, or forecast their future distributions in response to anthropogenic changes in climate and land use. Notable exceptions include species distribution models (SDMs) of *Dioscorea* and *Panax* (the former is a source of contraceptive compounds[6]; the latter is a root used in traditional Chinese medicine for therapeutic treatments for cancer, diabetes, and cardiovascular diseases[79,80]). Although clinical studies provide reasonable promise of *Panax* for treating patients with cardiovascular and metabolic diseases, larger-scale clinical trials are needed to substantiate its therapeutic effectiveness[81–83].

By identifying suitable areas and climatic parameters where medicinal plant species are found today, SDMs can delineate areas where these species may be found or cultivated in the

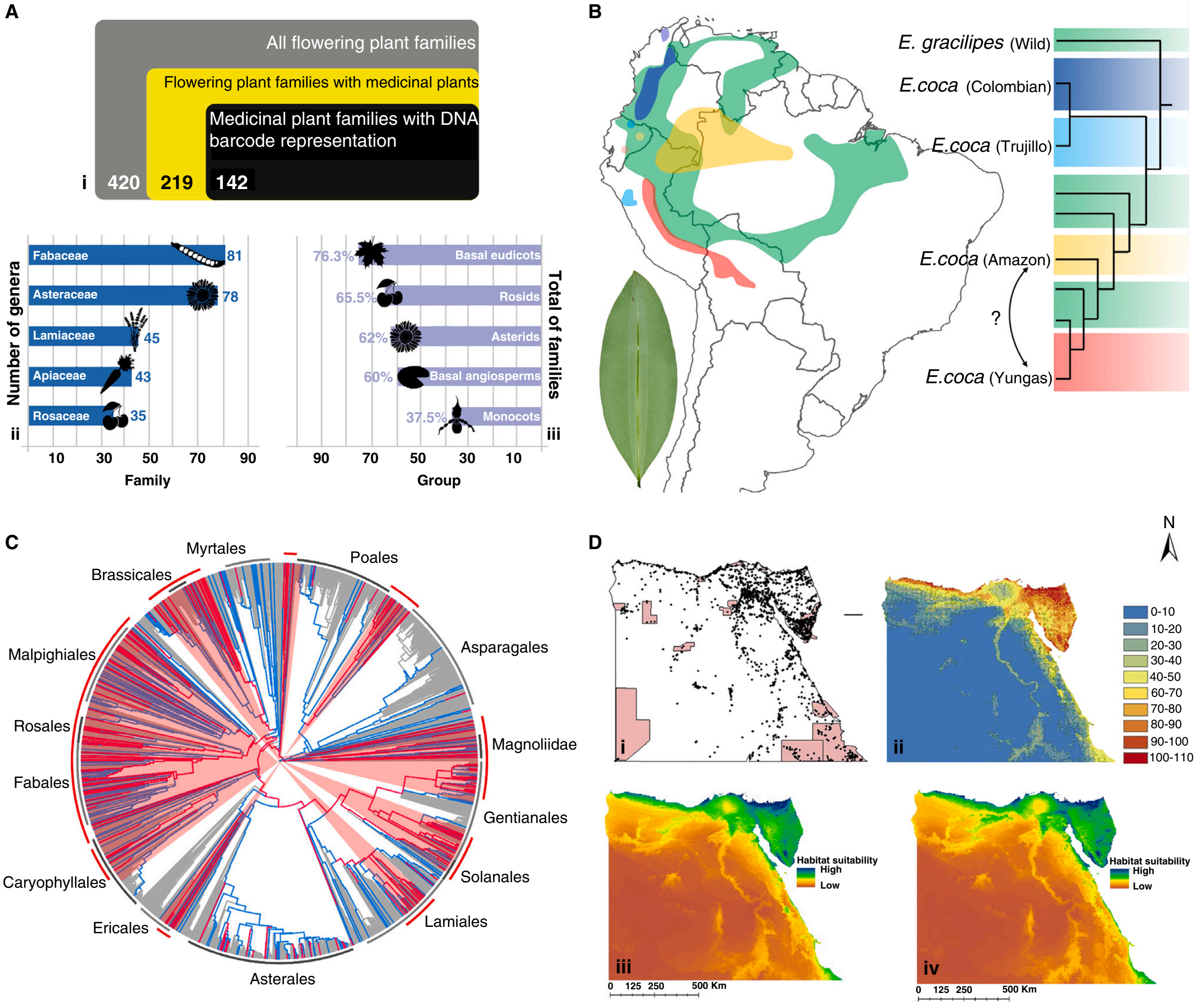

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Figure 2. Evolutionary ecology provides novel insights into the origin, persistence, and future distributions of medicinal plants.
(A) A recent survey of flowering plant DNA barcoding from medicinal plants (graphs based on data from Yu *et al.*[50]). (i) Box-in-box plot illustrating the total number of flowering plant families relative to the subset of families that include medicinal species, and those medicinal plant families with at least one DNA barcode available; (ii) bar plots illustrate the five families that include the most medicinal plant genera; and (iii) the percentage of medicinal plant families across major groups of angiosperms for which at least one species in that family has a DNA barcode. Note that these coarse family- and genus-level summaries hide the fact that most medicinal plant species have yet to be barcoded. (B) Extensive sampling from herbarium collections and phylogenomic analyses to elucidate the origin and identity of coca — the source of many medicinal alkaloids and flavonoids, including cocaine hydrochloride — revealed that all modern varieties of coca used by humans were domesticated from within the single wild species *Erythroxylum gracilipes* Peyr. The domesticated *Erythroxylum coca* Lam. is polyphyletic and represented informally by various lineages (Trujillo/Colombian, Yungas, and Amazon), suggesting multiple independent origins of this domesticate. The most ancient domestication event likely occurred in northwestern South America (Trujillo/Colombian); a more recent, second domestication event occurred in southeastern Peru (Yungas); and a possible third event took place in the Amazon basin (Amazon). Such findings are important for guiding efforts to understand the molecular, biochemical, and ethnopharmacological origins of these domesticates. (Leaf: © Dawson White; map redrawn from White *et al.*[184], with permission of Oxford University Press.) (C) Phylogenomics identified evolutionary 'hot zones' of species with reported antimalarial use in the flora of Latin America (adapted from Milliken *et al.*[70]). Lineages that include an overrepresentation of species with purported antimalarial properties are highlighted in red; lineages including at least one species with a reported antimalarial use, but that are not overrepresented phylogenetically, are highlighted in blue. (D) (i) Distribution of 114 Egyptian medicinal plant species[185]; (ii) their present-day species richness distribution; and (iii, iv) two of the most pessimistic future climate habitat suitability scenarios. The small differences between them[185,186] are cause for optimism. (Adapted from Kaky and Gilbert[185] and Kaky *et al.*[186].)

future. For example, the outlook for future habitat suitability for medicinal plants in Egypt is reasonably optimistic (Figure 2D). In contrast, ranges of medicinal plants in South Africa are expected to contract[84]. These investigations illustrate the value of SDMs while highlighting the need for broader assessments and forecasts of the climatic and geographical ranges of these species; they also provide the basis for linking phylogenomic investigations to SDMs in novel ways[85].

Medicinal plant trait ecology

Functional traits impact species fitness by affecting growth, reproduction, and survival[86]. They have been used widely in macroecology but rarely studied in medicinal plants. Insights from 'origin stories' such as those mentioned above for coca (Figure 2B) and cannabis are essential starting points for linking trait data with phenotypic, chemical, or genetic factors involved in early use and domestication of medicinal plants. Trait data also can help identify key contrasts between wild and domesticated species. A central challenge is the identification of the key traits that rendered these plants appealing and 'pre-adapted' them for human use. Functional trait ecology plus phylogenomic analyses also can help identify temporal and spatial sequences of selection on those plant traits that captured the initial attention of humans, and illuminate the order and direction in which those traits have been shaped from antiquity to the present. Such approaches have been applied recently to important crop species, such as maize and grape[87,88], but are largely lacking for medicinal plants.

Molecular biology and biochemistry

As an integrated discipline, molecular biology and biochemistry involves the discovery and description of the chemical and physical properties of biological molecules and deciphering the complex array of chemical reactions occurring in cells[89]. Its many applications have a proven track record in expanding our understanding of the structure, function, and regulation of genes that produce molecules of pharmacological importance.

Curative chemistry: Medicinal plant metabolites

Plants produce a vast array of chemical metabolites that regulate interactions with their environment[90] and which are used medicinally[12,13]. However, few of these metabolites are the product of primary metabolism that is essential for growth, development, and other vital activities. Instead, many of these metabolites are secondary (or specialized) ones derived from intermediate steps of primary metabolism[91,92]. These secondary metabolites are found in different plant organs at concentrations dependent on their points of origin and transport, both of which are largely unknown for most plants. Moreover, regulation and production of secondary metabolites can be induced by, for instance, time of day, climate, soil composition, post-harvest processing, and storage conditions[75,93–95]. Many of these metabolites also deter herbivores[96], frequently by targeting their central nervous system and altering their sensory perception[97]. Humans have co-opted these metabolites (among many others) for a variety of purposes. Examples include caffeine from coffee (*Coffea* spp.), nicotine from tobacco (*Nicotiana* spp.), and galantamine for treating Alzheimer's dementia from snowdrops (*Galanthus* spp.)[98]. Indeed, natural products, including those derived from plants, represent 84% of approved drugs for diseases pertaining to the central nervous system, but only 20 natural products provide 400 central nervous system-approved medicines[98].

Despite their importance, only a small percentage of the phytochemical properties of plant metabolites have been explored[99,100]. High-throughput screening to conduct large-scale, untargeted metabolomic investigations shows promise for scaling these efforts. State-of-the-art liquid chromatography high-resolution mass spectrometry and bioinformatics can be used in tandem to characterize spectral signatures and perform metabolite annotation for large arrays of plant extracts[101–104]. Combining such metabolomic investigations with network analyses and phylogenomic evidence (summarized in Evolutionary Ecology) when sampling broad clades of plants with known bioactive compounds is emerging as a promising direction for further scaling these efforts[9,105]. Untargeted metabolomic investigations can be augmented further with deuterium labeling to identify those plant organs where metabolite accumulation is greatest[106]. This approach is particularly relevant for field investigations of metabolites of the many large, long-lived, woody plants that are medicinally important but are not readily amenable for laboratory or greenhouse manipulations.

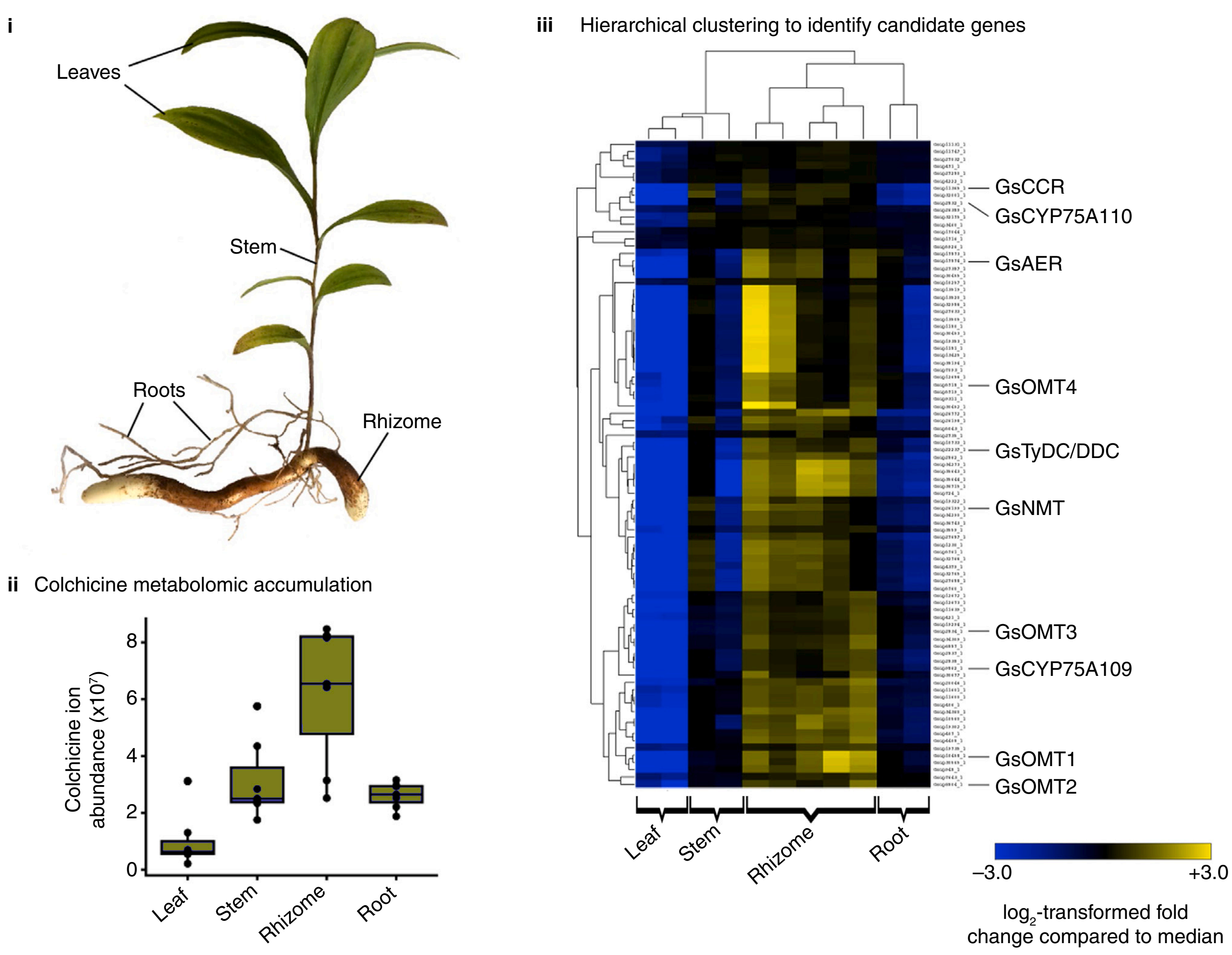
Another opportunity for innovation is the development of more accurate automated bioinformatic algorithms for identifying bioactive metabolites that rely heavily on well-annotated reference panels[103,104,107,108]. Such data increasingly are being mobilized online by academic–commercial partnerships to create massive open-access databases containing thousands of plant metabolites[101,109]. These efforts warrant expanded sampling from living plants in nature, but other opportunities could stimulate these efforts further. For example, herbaria are an underutilized resource for profiling plants for small metabolites. Additional validation is necessary to support the use of herbarium specimens for metabolic profiling, but some small molecules are stable and preserved for decades or even centuries in herbaria[66]. Success on this front has been demonstrated by identifying phytochemicals for treating Alzheimer's disease[110]. Similarly, metabolites such as those found in *Salvia* species, which produce potent neuroactive molecules, have been characterized successfully from herbarium materials that are nearly 150 years old[111].

Medicinal plant genomics: Sequencing plant genomes of antiquity

Few medicinal plants have been sequenced to date, and genomic investigations of medicinal plant species lag far behind those of model species and crops[112–115]. Genomes (and associated transcriptomes and epigenomes) can be used to elucidate biosynthetic processes underlying metabolic pathways, gene interactions, and the regulatory mechanisms of small molecules useful for medicines. Such information also can be used to select for new varieties of improved medicinal plants or help transform this knowledge into scalable 'living factories' of bioactive compounds, as has been accomplished for the large-scale synthesis of opioids[116].

Genomic sequencing recently has revealed the genetic underpinnings of the tropane alkaloids (TAs) hyoscyamine and scopolamine in the nightshade family (Solanaceae), which includes tomatoes, potatoes, peppers, and eggplants[117]. TAs are important for treating neuromuscular disorders (e.g., Parkinson's disease), are used in anesthetics and analgesics, and have been deployed as antidotes to nerve agents in combat situations. In the Solanaceae, TA biosynthesis is facilitated by a common gene cluster involving gene duplications that appears to have evolved early in the diversification of this family[117]. In contrast, TA biosynthesis follows a different and evolutionarily independent pathway in coca and its relatives (in the family Erythoxylaceae)[118]. The unique enzymatic properties in coca that likely provide its associated euphoric properties are absent in Solanaceae, lending additional evidence for the independent evolution of the

A Transcriptomic and metabolomic profiling to identify candidate genes for colchicine biosynthesis



B *Agrobacterium*-mediated transient expression in *Nicotiana benthamiana*

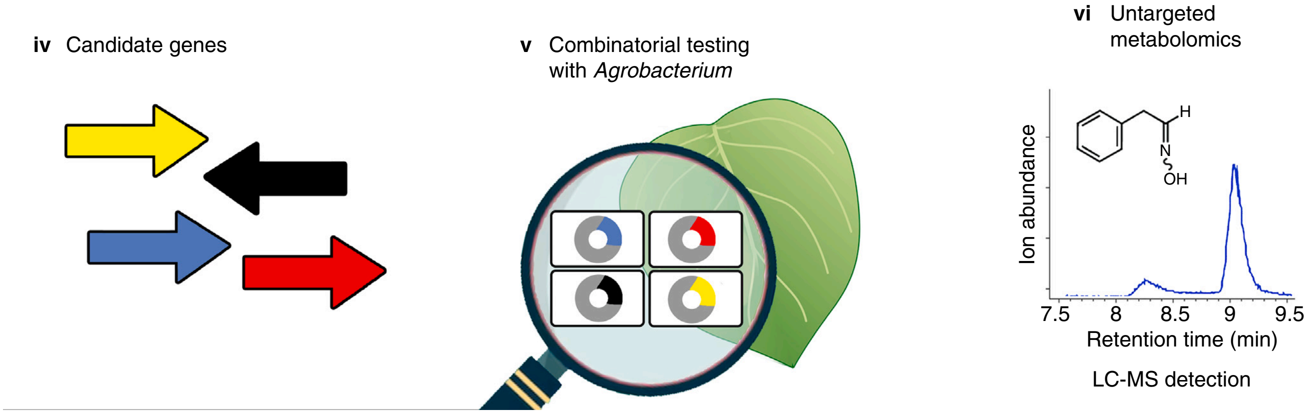


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Figure 3. Molecular biology and biochemistry facilitate more rapid understanding of medicinal plant biosynthetic pathways.
(A) Metabolomic and transcriptomic profiling used to unlock the biosynthesis of key small metabolites. (i) Biosynthetic pathway genes in plants are often co-regulated and can be interrogated across tissues and developmental timing. (ii) Sampling can be complemented with simultaneous metabolomic assessments across space and time to discern the metabolic accumulation for each tissue and identify the active site of biosynthesis (here, the rhizome). (i and ii redrawn from

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biochemical pathways for TA synthesis. Similarly, independent origins of cannabinoid biosynthesis using whole genomic data also have been recently demonstrated in *Helichrysum umbraculigerum* Less., a South African member of the sunflower family (Asteraceae)[119]. Exploring convergent and divergent pathways that yield similar metabolic products elucidated by our understanding of plant evolutionary relationships is an active and exciting area of research.

Unlocking plant biosynthesis to reveal active molecules using novel metabolomic and transcriptomic pipelines

Characterization of complete biosynthetic pathways has contributed fundamental insights to our understanding of human physiology; for example, the ability of humans to detect heat and pain was discerned from exploring the biosynthesis of the plant alkaloid capsaicin[120]. However, elucidating biosynthetic pathways in plants is challenging. Few complete biosynthetic pathways have been characterized for plant-derived medicines[100,121]. Completely characterizing biosynthetic pathways historically has required complete genomes (which in plants can reach at least 30 GB[122]) and we also lack starting candidate genes thought to be involved in the production of most medicinal molecules[121,123]. These challenges have translated to long delays in characterizing the complete biochemical pathways of medicinal plant metabolites. For example, it took two decades to fully characterize the biosynthesis of opium[116]; complete documentation of biosynthesis of paclitaxel (one of the most expensive drugs to manufacture) and other chemotherapeutic compounds remain incomplete despite their identification in the 1960s[100].

Numerous approaches facilitated partly by approaches from evolutionary ecology, including phylogenetic gene clustering, quantitative trait locus assessments, and genome-wide association analyses, have been developed to reduce the number of candidate genes required to explore gene function and biosynthesis[100]. Nett *et al.* recently demonstrated a promising method that obviates many of the obstacles outlined above[121]. Their co-expression workflow combines metabolomics with transcriptomics to localize the production of key metabolites and gene expression, as well as hierarchical clustering and chemical logic to identify likely candidate genes important for biosynthesis (Figure 3). This method, which requires no prior knowledge of key biosynthesis genes or a complete genome of the host plant, was deployed successfully to synthesize colchicine *in vitro* from *Gloriosa* lilies. This alkaloid is widely used to treat inflammatory disorders (e.g., gout, Mediterranean fever, and pericarditis)[124,125]. Once candidate genes were identified, functional properties of each of these gene targets were determined using agrobacteria multiplexed into transgenic plants (*Nicotiana benthamiana* Domin). This transient expression system facilitated precise characterization of the cascade and sequencing of metabolites involved in the stepwise production of colchicine. Nett *et al.* also assessed key neuroactive compounds in the club moss *Phlegmariurus tetrastichus* (Kunze) A.R. Field & Bostock[123]. Not only did these researchers characterize early and late metabolites involved in neuroactive compound synthesis, but they also identified key candidate genes associated with the production of a rich suite of metabolites, including 16 alkaloids[126]. O'Connor has also applied advanced -omics technologies to detect transcripts and metabolites within single cells, most recently interrogating biosynthetic pathways in *Catharanthus roseus*, a leading source of anticancer drugs[127].

Ethnopharmacology

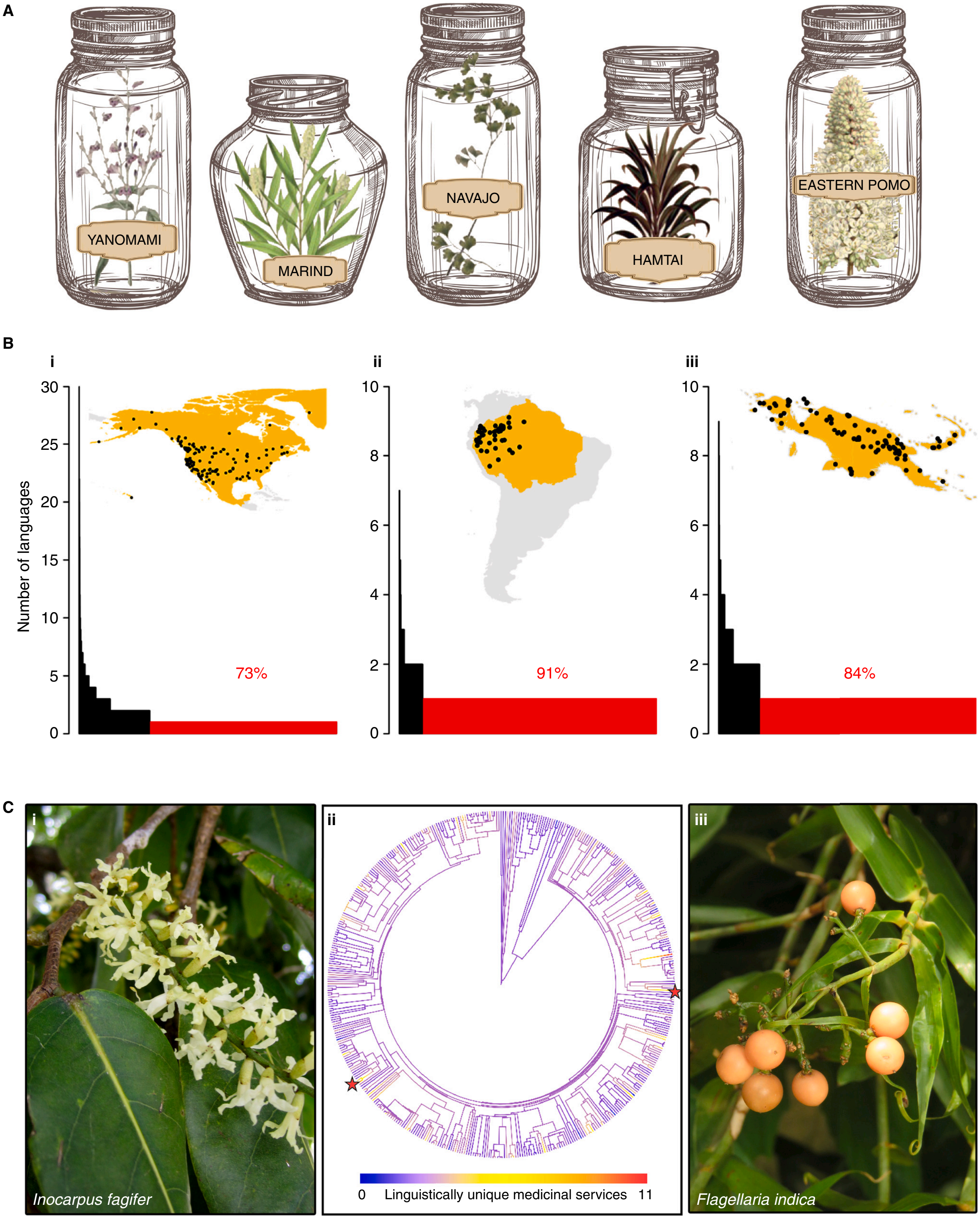
Ethnopharmacology involves the observation and description of biological activity of traditional or folk medicines[17,21,128]. This work is derived from the field of ethnobotany, which is the study of traditional knowledge and customs related to a people's use of their native plants[129]. Integrating ethnopharmacological data and traditional knowledge from Indigenous communities is central to identifying medicinal plants and developing conservation strategies for them that include all stakeholders[130,131]. In addition to identifying key traits essential for some of the phylogenetic analysis outlined above, ethnopharmacology also has helped to guide metabolomic drug discovery. Specifically, -omics technologies have uncovered unconventional therapeutic applications of blood-activating Chinese botanical drugs used in traditional Chinese medicine in combination with antiplatelet drugs[132]. Similarly, Salem *et al.* designed a study to confirm the *in vivo* antihypertensive capabilities of *Hibiscus sabdariffa* L., a folk remedy used since ancient times[133].

Plants as partners

Plant-derived compounds, either unprocessed or in a complex matrix following the raw extraction of their active ingredients (e.g., in a brewed tea of leaves containing medicinal properties), have been used by different peoples for millennia[9,10,134]. Traditional medicines have provided origins and inspirations for developing important conventional medicines[4,26], including quinine and artemisinin for malaria[135,136], and digitoxin for cardiovascular disease[137–139]. Indeed, among the ≈60% of the ≈14,000 species of plants summarized in the NAtural PRoducts ALERT[140] database that have been examined biologically or chemically, 75% of the subset that involve plant-derived products prescribed as medicines are used in ways that largely mirror their traditional uses[128,141].

Research into the ethnopharmacology of medicinal plants must center Indigenous perspectives. Indigenous narratives and practices that form the basis for many drugs derived from plants and other organisms (e.g., fungi) include intimate natural-history knowledge, which species or populations are used medicinally, the details of how and when relevant species are cultivated and harvested, and how they are prepared[17,142]. Indigenous knowledge also encompasses the cultural, spiritual, political, and economic relevance of medicinal plants, including the oral traditions relating to the origins of these species and their cultural significance. Many oral traditions recount the origins of medicinal plants[143,144], which can be analyzed in conjunction

Nett *et al.*[121] with permission from SNCSC.) (iii) The transcriptomic and metabolomic data are then assessed using hierarchical clustering and chemical logic to determine likely candidate genes for functional evaluation. (B) Functional evaluation of candidate genes using *Agrobacterium* and *Nicotiana* tomato plants (adapted from Jacobowitz and Weng[100]). (iv) Eight candidate genes from *Gloriosa superba* were identified for exploration (only four are represented here and indicated by the differently colored arrows); (v) these genes were transformed and multiplexed into *Nicotiana* using *Agrobacterium*; and (vi) key colchicine precursors were identified using LC-MS to characterize the complete biosynthetic pathway of this plant medicine.



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with their interpretations by evolutionary ecologists to link such plant trait knowledge with the phylogenetic distribution of plants. Some neuroactive plant medicines are considered sacred, even referred to as entheogenic, or 'god revealing'[145]. Such plants are gaining renewed interest in Western culture for their potential therapeutic value, but crucial traditional information is often overlooked. For example, Indigenous use of tobacco differs from Western use and is notable for its reduced danger and addictive properties[146]. Ignoring Indigenous applications and uses of medicine also may neglect potential therapeutic benefits of these medicines, such as the emetic and purging properties of some plant-derived preparations[147].

The interconnectedness of medicinal plant biodiversity and Indigenous linguistic diversity

The biodiversity of medicinal plants is inextricably linked with biocultural heritage and sophisticated medicinal plant knowledge is encoded in Indigenous languages[142,148], which are largely transmitted orally[149]. The ambitious Biocultural Diversity Mapping Project uses plant and language data to visualize the strong positive correlation between areas of high plant species diversity and high language diversity[150].

Using aggregated biodiversity and biocultural data, Cámara-Leret and Bascompte discovered that Indigenous knowledge of most individual medicinal plant species is restricted to only a single language[151] (Figure 4). By combining a data set that included thousands of plants and their uses with linguistic data from >200 languages spanning North America, northwestern Amazon, and New Guinea, Cámara-Leret and Bascompte concluded that the threat to the rich Indigenous knowledge of medicinal plants from language loss is far greater than the threat from species loss. They further concluded that the Americas represent an Indigenous language hotspot where medicinal plant knowledge is strongly linked to threatened languages[151].

This study further highlighted the potential power of large-scale analyses using aggregated ethnobotanical data combined with data normally used exclusively by evolutionary ecologists (i.e., species identities, distributions, and phylogenetic relatedness). Despite their importance, such ethnobotanical data are mostly inaccessible; they are mostly not digitized, buried in unindexed literature and museums, or exist as Indigenous knowledge that is widely ignored by conventional Western scholarship[152]. An interdisciplinary approach combining diverse data streams (ethnopharmacological data, language diversity, and plant phylogenies) can reveal important phenomena such as 'ethnobotanical convergence', whereby related evolutionary hot zones within the plant tree of life have been discovered independently by distant human populations yet used for similar medicinal purposes[153].

Globalization of traditional medicine and Indigenous rights to benefits and participation

Equitable inclusion of Indigenous peoples as key stakeholders, knowledge contributors, and participants in interdisciplinary research on medicinal plants is non-negotiable. Indigenous communities should be engaged as active participants and team members in all aspects of medicinal plant science outlined above, ranging from making taxonomic decisions concerning the delineation of medicinal plant species[154] to helping to establish comparative genome-sequencing workflows[155]. Best practices for developing these partnerships are outlined in the International Society of Ethnobotany's Code of Ethics[156] and the recent Indigenous Research Agreement for genome sequencing[157]. Indigenous peoples, who represent <5% of the global population[158], steward or govern nearly 40 million km^2 of land and inland waterways in 82 countries. These lands, which house large numbers of medicinal plant species, include 25% of Earth's land surface, 40% of its protected land areas and ecologically intact landscapes, and 36% of its intact forests[158,159]. Historical pursuits to explore medicinal plants and bring them to a larger audience are rife with examples of the extraction and exploitation of Indigenous peoples and their lands and knowledge without any benefits accruing to these communities[160]. These pursuits also span the long history of colonial exploitation and are plagued by issues of systematic racism and cultural biases against Indigenous peoples.

Traditional knowledge and the livelihood it brings to Indigenous communities are handed down over generations and threatened by commercial profiteering that reduces biocultural knowledge to commodities and privatized intellectual property rights (IPRs) that motivate wrongfully filing patent applications[152]. Thus, protecting Indigenous rights and the countries to which they belong is essential in these engagements and should always strive to return value to these countries and communities[161]. Sharing of benefits is expected by international accords — especially the Nagoya Protocol, which identified clear policies around access and benefit sharing (ABS) meant to ensure the prior informed consent of Indigenous communities and to guarantee their receipt of benefits. The nature of traditional knowledge, which is often 'owned' by the community rather than by a single individual, does not fall neatly into Western legal conventions of IPRs. This issue is compounded by the proliferation in recent years of digital sequencing information, which is meant to be open access and allows users to

Figure 4. Ethnopharmacological investigations reveal inextricable linkages between medicinal plant biodiversity and Indigenous linguistic diversity.

Medicinal plant biodiversity and indigenous linguistic diversity are inextricably linked (reproduced from Cámara-Leret and Bascompte[151]). This large ethnopharmacological assessment spanned North America, northwest Amazonia, and New Guinea and included ≈3,500 medicinal plant species representing ≈12,500 plant medicinal 'services' (e.g., treatment for digestive illness), and ≈240 Indigenous languages. It demonstrated strikingly high associations of linguistic uniqueness associated with medicinal plant uses in all regions explored, with 73%, 91%, and 84% of the species in North America, northwest Amazonia, and New Guinea, respectively, each being cited by only one language[151]. Threatened languages supported 86% and 100% of all unique medicinal plant knowledge in North America and northwest Amazonia, respectively. (A) Medicinal plants form the basis of regional pharmacies and are represented by each jar and labeled according to their associated languages. (B) Knowledge about most individual medicinal plants is associated with only a single language. Histograms illustrate the number of Indigenous languages in (i) North America, (ii) Northwest Amazonia, and (iii) New Guinea; red bars show medicinal plant knowledge associated with only a single language; dots on maps indicate distribution of languages. (C) Phylogenetic distribution of unique medicinal plant knowledge in the flora of New Guinea. Illustrations and corresponding numbers show medicinal plants with a high number of distinct medicinal services; the 'warm' colors of the phylogeny indicate multiple uses for most of these species. (Panels A, B, and Cii from Cámara-Leret and Bascompte[151]; *Iconocarpus fagifer*: © Plantaholic Sheila/Flickr; *Flagellaria indica*: © Reuben C. J. Lim/Flickr.)

circumvent the Nagoya Protocol. For these reasons, digital sequencing information and benefit sharing are topics of much unresolved debate in recent Conferences of the Parties on the Convention on Biological Diversity (CBD). Strategic developments of these policies, together with the exploration and enforcement of novel IPR regulatory tools and enhanced models of collaboration[162,163], will have a positive impact on the future study of medicinal plants by researchers and their relations with communities who steward medicinal plant knowledge.

Protecting medicinal plants

Recognizing the past, present, and future value of plants for preventing and treating diseases is a crucial first step toward responsible stewardship of medicinal plant biodiversity for future generations. Integrative research on medicinal plants should lead to a greater focus on conserving genetic, phenotypic, chemical, and biocultural diversity, especially near their centers of origin, where such diversity is likely to be high, and on revealing and preserving the complicated history and relationships between humans and medicinal plants. Key challenges to conserving medicinal plants include biodiversity loss, overharvesting, climate change, and loss of traditional knowledge[164,165].

Conservation and protection of medicinal plants is especially important because at least two-thirds of medicinal plants continue to be harvested from the wild and many medicinal compounds are derived from species that grow and accumulate essential compounds slowly[26,165]. Populations of many of these species are small or even rare and endangered[166–168], and overharvesting has had demonstrable impacts on the shape and size of some of these plants[169]. For many of these species, wild harvesting is unsustainable and has already contributed to drastic population declines and extinction. The most famous example of this may be the extinction of silphium (Apiaceae; likely a *Ferula* spp.) — thought to be the first recorded extinction of a species attributable to humans — that may have been harvested to exhaustion over two millennia ago by the Romans who used it as a contraceptive and an abortifacient[170,171]. Related modern examples include the overharvesting of Pacific yew for its anticancer properties[48,172] and American ginseng (*Panax quinquefolius* L.) for treatments of hypertension and respiratory infection, especially in Traditional Chinese Medicine[173].

To avert future losses, we suggest six actions to help preserve bioculturally important medicinal plant species. First, we must establish a germplasm repository focused on breeding, research, and *ex situ* conservation of medicinal plants of the world[128]. This global effort should be complemented by coordination of regional gardens that support and sustain communities where medicinal plants are used most actively[174] and serve to educate members about sustainable harvesting practices[164].

Second, we should expand and coordinate comparative genome sequencing to facilitate conservation and continued exploration of medicinal plant species[114]. Identifying genetic and biosynthetic pathways of plant metabolites central to human health should remain a high priority. Ongoing large genomic initiatives, such as the 10,000 Plants Genome Project[175], can amplify these efforts.

Third, it is necessary to scale and broaden research characterizing the small metabolite diversity present in medicinal plants[101,109], especially within and among plant clades that have been demonstrated to have therapeutic value. Phylogenetically guided exploration can help pinpoint possible substitutes for species at risk of over-harvesting. Because medicinal plants sometimes have large native ranges, care should be taken when using substitute species to avoid transferring pressures to more range-restricted species that may be more susceptible to extinction[5].

Fourth, we should preserve hotspots of biocultural heritage, especially where linguistic diversity is greatest, to staunch the loss of unique medicinal plant knowledge[151].

Fifth, we need to protect the natural matrix in which medicinal plant species coexist with people. Approximately 40% of plant species face extinction in the coming decades[176]. Medicinal plants can be used to highlight the need for conserving larger ecosystems in which these species occur.

And finally, we should recognize and come to terms with the colonial and extractive legacy of developing plant-based medicines and of plant exploration more broadly[177,178]. To achieve this goal in a more unified and inclusive way, we must acknowledge and avoid the pitfalls and obstacles of our past that are a consequence of exploitation, overconsumption, and greed. Biotechnological innovations such as large-scale plant tissue culture have already proven successful in producing plant-derived drug therapies (e.g., paclitaxel) while avoiding over-harvesting, providing one example of combating such extractive legacies in medicine[179]. Improvements in international treaties and legal frameworks, including novel IPR regulatory tools and enhanced (and enforced) models of collaboration, will ensure sustainable innovation and protect indigenous communities and their knowledge[162,163].

Conclusions

Since hominins evolved, they have used plants for food, shelter, and medicines. Just as with animals, humans have exerted selective pressures on plants, identified new varieties, and domesticated them[180]. However, we suggest that the relationship between humans and medicinal plants may be more than one of identification, utilization, domestication, and harvest. Rather, we hypothesize that medicinal plants and people should be viewed as partners whose relationships involve a complicated and poorly explored set of (socio)ecological interactions that extend from domestication to commensalisms and mutualisms. In short, medicinal plant species are not just chemical factories for extraction and exploitation. Rather, they may be symbiotic partners that have shaped modern societies, improved human health, and extended human lifespans.

A proper test of our hypothesized symbiosis involving medicinal plants and humans will require us to combine evolutionary ecology, molecular biology & biochemistry, and ethnopharmacology in bold and creative new ways. The interdisciplinary research agenda that we have proposed here should allow us to define when, where, why, and how symbioses between medicinal plants and humans arose. The latter — *how* these interactions arose — is the least understood and most challenging component of our hypothesis. One avenue for exploration is to characterize ‘medicinal’ use of plants by other animals. Ecologists, ethnopharmacologists, and anthropologists could jointly explore the extent to which humans have used observations of ‘nature’ to select medicinal plants (zoopharmacognosy)[12,13,181,182]. For example, leaf-cutter ants have symbiotic associations with actinobacteria, which produce antibiotics that help to eliminate infections in the fungal gardens these ants cultivate for food[183].

We can also ask whether domestication leads to mutual dependency. For example, while cultivating plants for their medicinal use (e.g., opium poppy, cannabis, digitalis), we have not only shaped varieties, selected strains, and propagated and protected them, we have also greatly expanded their ranges. The plants, in turn, have provided humans with enormous health benefits (and in some cases also detrimental addictions). Such socioecological mutualisms that reflect plant biochemistry have received relatively little investigation by evolutionary ecologists or ethnopharmacologists.

Transdisciplinary efforts will rapidly advance our understanding of when, where, why, and how medicinal plant species originated and how their use has evolved in different socioecological contexts. The prioritization of medicinal plants in biodiversity-oriented investigations not only will enhance the discovery of future lifesaving compounds, but also will increase the recognition, value, and reciprocity of Indigenous and Traditional knowledge, fortify a socioecological currency vital to the preservation of cultures and natural ecosystems, and provide insight into the history and expressions of the human species.

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AUTHOR CONTRIBUTIONS

C.C.D. conceived the idea for this paper and wrote the manuscript; P.C. revised and approved the draft.

DECLARATION OF INTERESTS

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