Evaluating natural medicinal resources and their exposure to global change

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Medicinal plants and their bioactive molecules are integral components of nature and have supported the health of human societies for millennia. However, the prevailing view of medicinal biodiversity solely as an ecosystem-decoupled natural resource of commercial value prevents people from fully benefiting from the capacity of nature to provide medicines and from assessing the vulnerability of this capacity to the global environmental crisis. Emerging scientific and technological developments and traditional knowledge allow for appreciating medicinal plant resources from a planetary health perspective. In this Personal View, we highlight and integrate current knowledge that includes medicinal, biodiversity, and environmental change research in a transdisciplinary framework to evaluate natural medicinal resources and their vulnerability in the anthropocene. With Europe as an application case, we propose proxy spatial indicators for establishing the capacity, potential societal benefits, and economic values of native medicinal plant resources and the exposure of these resources to global environmental change. The proposed framework and indicators aim to be a basis for transdisciplinary research on medicinal biodiversity and could guide decisions in addressing crucial multiple Sustainable Development Goals, from accessible global health care to natural habitat protection and restoration.

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Introduction

> "[Patroclus] then crushed a bitter herb, rubbing it between his hands, and spread it upon the wound; this was a virtuous herb which killed all pain; so the wound presently dried and the blood left off flowing."
>
> *Homer, Iliad, Book XI, ~8th century BCE*

Human health has been inextricably linked to the use of herbal medicines for millennia, making natural medicinal resources one of the oldest contributions of nature to human wellbeing.[1,2] However, increasing global change in the anthropocene is jeopardising the future of these contributions to societies.[3,4] Archaeological evidence suggests that our palaeolithic ancestors might have relied on knowledge of the location and use of medicinal herbs for their survival;[2] the therapeutic applications of numerous plant species have been extensively documented since the onset of the first ancient civilizations through to modern history.[5] In the past four decades, despite the disproportionally large investments and research focus on synthetic drug discovery, approximately half of the globally approved pharmaceutical drugs have been derived from or inspired by natural products.[6] In the past decade, scientific and technological developments in screening plants for bioactive compounds have revitalised interest in natural products and the ability to explore the biochemical diversity of nature as a major medicinal resource.[6–8]

The prevailing notion of nature as a rich source of and inspiration for novel medicines has led to substantial benefits for humanity. Yet the appraisal of medicinal plants solely as an ecosystem-decoupled natural resource of commercial value, as well as the ever-increasing market demand for herbal medicines, has led to overexploitation of medicinal species, making many natural populations almost extinct.[3,4] Land use and climate change are further increasing the extinction risk of species and their bioactive compounds, threatening both ecosystems and the future of human health.[9,10]

Bioactive compounds produced by plants and their endophytes are integral parts of ecosystems, participating in fundamental ecological processes[11,12] and contributing essential health benefits to populations globally.[13,14] The current lack of transdisciplinary frameworks for evaluating medicinal biodiversity as a central component of planetary health[15] hinders the ability to sustainably manage that biodiversity and fully benefit from its potential contributions to human societies. Such a framework is of the utmost importance to protect these contributions from the ongoing effects of the environmental crisis that is rapidly eroding biodiversity for future generations worldwide.[16]

In this Personal View, we assess current knowledge and future research directions for the implementation of a framework to evaluate medicinal plant resources and their environmental threats in future scenarios of socioeconomic development. The proposed framework is based on the theoretical foundations of the Social-Ecological Systems[17] and the Nature's Contributions to People[16] concepts and aims to motivate transdisciplinary research to achieve major Sustainable Development Goals, from accessible global health care to natural habitat protection and restoration. With Europe as an application case, we propose a set of proxy spatial indicators that integrate a diverse array of data on biodiversity, medicinal, environmental, and financial attributes. These indicators show the potential of natural medicinal resources that can be provided by plants (figure 1), from resource capacity to potential societal benefits and values, and assess the exposure of these resources to the ongoing environmental crisis.

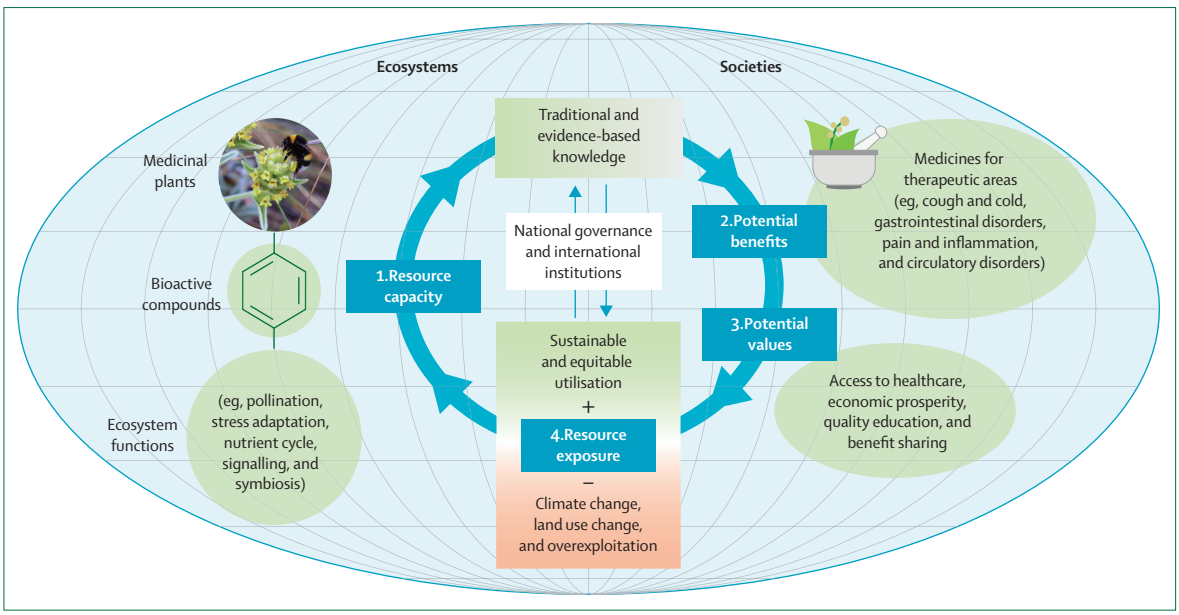

Figure 1: **A planetary health perspective of natural medicinal resources**
The proposed conceptual framework that links ecosystems and human societies via the interaction between traditional and evidence-based knowledge and the sustainable and equitable use of medicinal plants. Resource capacity, potential benefits, potential values, and resource exposure are the four elements that can be approximated by the proposed spatial indicators.

The overlooked dimensions of medicinal plant resources

Evidence-based integration of herbal medicines into health care

Herbal medicines (ie, medicines exclusively containing vegetable material) are the oldest and most direct way of using the therapeutic properties of nature.[4,5] According to WHO, traditional and herbal medicines of proven quality, safety, and efficacy are crucial for ensuring that all people have access to primary health care around the world.[13] The ever-increasing public need for accessible, nature-based health solutions led to the development of an updated WHO Traditional Medicine Strategy 2014–23, which aimed to encourage clinical research for herbal medicine and encourage member states to consider herbal medicine as an integral part of their health systems.[13] In a 2019 WHO global survey, the majority of member states (110 of 179) formally acknowledged that their population uses herbs as a health resource.[18] Moreover, the number of member states implementing regulations on herbal medicines had steadily increased since 1999 (124 in 2018).[18] Major agencies, such as the European Medicines Agency (EMA),[19] have made notable progress in providing guidance to facilitate herbal drug development and promote their safe and efficient application. However, the number of registered clinical studies evaluating herbal medicines from 2016 to 2019 globally was only 1% of all registrations.[20]

Although scientific evidence in support of herbal therapies is accumulating, considerable progress remains to be made in the implementation of herbal medicines as a primary nature-based health solution. In the 2019 WHO report on traditional medicine, which included but was not limited to herbal medicines, the major challenges that member states encountered with regard to regulatory issues were the lack of research data, followed by the lack of financial support for research, the lack of mechanisms to monitor safety, and the lack of education and training for professionals.[18] These findings show that the increasing need for herbal medicines is not accompanied by sufficient research efforts and economic support, which maintains the gap between traditional knowledge of medicinal biodiversity and evidence-based integration of this knowledge into modern health care. At the same time, the predicted extinction of up to 30% of indigenous languages and cultures by the end of the 21st century is threatening unique knowledge of medicinal plants, which compromises the capacity to explore the wealth of information accumulated throughout human history.[21]

Science and technology unlock the potential of the plant kingdom

Despite the recognised significance of plant bioactive compounds for human health, substantial knowledge gaps remain regarding their occurrence and prevalence across the plant kingdom and their potential role as medicinal resources. Plants and their endophytes contribute approximately 70% of all known natural products,[22] including major pharmaceutical drugs, such as morphine from opium poppy as a painkiller, paclitaxel from yew as a chemotherapeutic agent, and the Nobel-Prize-winning artemisinin from sweet wormwood as an antimalarial

agent.[14] However, of about 374 000 plant species that humanity is currently aware of,[23] approximately 15% have been investigated phytochemically and only 6% have been investigated pharmacologically.[24]

Historically, the method of selecting plants as potential medicinal sources relied mostly on knowledge from the scientific fields of ethnobotany, chemosystematics, and ecology, restricting research to a small number of species or regions with relevant previous information.[24] However, emerging approaches that integrate these scientific fields with the ever-increasing amount of environmental data reveal both the distribution of bioactive compounds across geographical regions and taxa and their underlying environmental and evolutionary drivers. The predictive power of these interdisciplinary approaches is exemplified in studies from 2020 and 2021 on the flora of Java[25] and the Swiss Alps[26] that integrated species distributions, phylogenies, phytochemical compositions, climate data, and soil data to predict species assemblages of potentially high medicinal value.

Characterising bioactive compounds of pharmacological relevance in complex crude plant extracts has been another major limitation in the development of evidence-based phytotherapy.[8,14,27] However, rapid scientific and technological developments in the metabolite (ie, metabolomics) and genomic (ie, genomics) profiling of complex biological mixtures containing hundreds of thousands of compounds are revolutionising the prioritisation of crude plant extracts for downstream pharmacological and clinical investigations.[8,27] A notable example is the sequencing of the large and complex genome of yew to identify genes involved in the biosynthesis of the anticancer drug paclitaxel.[28]

Socioeconomic disparity threatens medicinal plants

Although scientific and technological progress provide solutions for the use of plants as a major health source, challenges related to their sustainable and equitable use might be harder to overcome. Often the popularisation of a plant, either as a herbal medicine or as a source of bioactive compounds for industrial drugs, is accompanied by increased international market demand leading to overexploitation of its natural populations and elevated extinction risk.[4,29] 60–80% of globally traded medicinal plants are harvested from their natural habitats, with an estimated trade value exceeding US$3 billion.[29] Approximately 365 medicinal plants are protected from overexploitation by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)[30] and approximately 1280 CITES-listed plant species are referenced in Kew's Medicinal Plant Names Services.[31] Of approximately 35 000 species of plants documented to be of medicinal use,[32] only about 5000 have been assessed by the International Union for the Conservation of Nature Red List of Threatened Species, with about 13% of them being categorised as threatened.[3]

Despite increasing efforts to regulate international trade, there are numerous documented examples of overexploited and threatened medicinal plants. One example, which is the subject of ongoing research, is ironwort (also known as mountain tea; figure 1). Ironwort includes several species of the genus *Sideritis*, mostly distributed in the Eastern Mediterranean region and the Balkans, with well known medicinal properties (ie, treating cough, cold, and gastrointestinal disorders).[33] The increasing commercial interest in these plants has led to overharvesting and the rapid decline of their natural populations over the past four decades.[9] Balkan countries have now included these plants in national red lists and trade directives to protect them. However, despite the regulations and numerous cultivations across the regions, illegal overharvesting of ironwort continues as seasonal herb picking is the only source of income for thousands of people in the Balkans.[34] This example highlights the socioeconomic roots of overexploitation (ie, the unregulated sourcing and economic disparity between the individuals or groups involved).

Because of the urgent need to protect and equitably use natural medicinal resources, sustainable cultivation and management systems need to be established in supplying regions. Permaculture and polyculture systems[35] that grow native medicinal plants are ways to elicit transformative change for sustainable and equitable sourcing. With traditional ecological knowledge, these agroecological systems aim to mimic or preserve the heterogeneity and biodiversity of natural habitats, thereby supporting a large number of ecological processes.[36] Furthermore, by engaging local communities, permaculture systems can replace the income from herb harvesting. For abundant medicinal plants that can be collected from their natural habitats, annually updated harvesting quotas based on frequent monitoring of natural populations and the socioeconomic status of local societies need to be efficiently implemented to improve sustainable management and restrict overexploitation.

Medicinal plants are involved in ecosystem functions supporting the wellbeing of nature

A largely overlooked aspect of the evaluation of nature as a medicinal source is the ecological role and function of the molecules providing therapeutic benefits. Accumulated evidence suggests that plant bioactive compounds used in medicine, specifically the products of secondary metabolism of species, happen as a result of interactions between plants and their ecosystems.[11] These secondary metabolites are integral to a large number of ecological and evolutionary processes, including species defence against biotic and abiotic stress, multispecies mutualistic relationships, and soil health, and their effects occur throughout ecological networks (figure 1).[11,12,37]

Secondary metabolites that are of pharmacological relevance exert a major protective mechanism against biotic and abiotic stress. The alkaloid nicotine found in tobacco plants, used both in modern industry and by Native Americans as a multipurpose traditional remedy, functions as an effective defence against phytophagous insects in nature.[38] The volatile 1,8-cineole produced by numerous plants, such as sage and eucalyptus, is used as a neuropathic pain inhibitor,[39] whereas in nature it prevents pathogenic infections in herbivore-damaged plant tissues.[40] Salicylic acid, a phenolic compound in the bark of white willow from which aspirin is derived,[41] is a plant hormone that regulates responses to low temperature extremes, droughts, and salinity.[42] The volatile sesquiterpene nerolidol, a potential treatment for neurodegenerative diseases[43] found in the essential oils of ginger and tea plant, is important in the modulation of species tolerance to cold stress and in plant–plant communication.[44]

Plant secondary metabolites also mediate species mutualistic interactions, such as pollination, seed dispersal, and plant–endophyte symbiosis, supporting ecological networks and biodiversity across taxonomic kingdoms. The promising anticancer agent geraniol,[45] an abundant monoterpene found in the essential oils of geranium and rose (among others), is integral as a precursor volatile compound in pollinator attraction, regulating species coevolution through pollen dispersal.[46] The sesquiterpene β-caryophyllene, reported to have anticancer and analgesic properties,[47] is found in numerous medicinal plants including common hop and piper and is apparently produced as an odorant in ripe fruits to attract frugivorous bats that act as seed dispersers.[48] Beyond the visible world, plants host abundant and diverse microbiota (ie, bacteria and fungi) and this symbiotic relationship modulates the production of secondary metabolites of medicinal value.[49] For example, bacterial diversity of the widely used *Echinacea purpurea* stimulates the production of secondary metabolites in the plant, directly affecting its therapeutic properties.[50]

An ecological role of plant secondary metabolites that is less studied is their involvement in affecting below-ground biodiversity. The release of pharmacologically important compounds from plants into soil affects the composition and activity of microbial communities responsible for fundamental ecological processes that govern ecosystem structure.[37] The presence of the widely distributed plant flavonoid, quercetin, appears to increase bacterial biodiversity in soils,[51] suggesting that it has a regulatory role in litter decomposition and the nutrient cycle. The effects of plant secondary metabolites on soil microbes might also define other ecosystem processes. For example, tannins found in the litter of poplar inhibit nitrogen fixation in the root system of alder, thus providing a competitive advantage to poplar for secondary forest succession.[37]

These examples are a small part of the reported ecological roles of plant bioactive compounds but highlight a crucial aspect of the sustainable management of medicinal biodiversity. The evaluation of natural medicinal resources should include not only the species-specific perspective, but also ecological communities and their metabolites as the agents providing therapeutic benefits.

Medicinal plants support societal wellbeing

Access to primary health care that is safe, effective, equitable, and cost-effective is a global priority to achieve the UN Sustainable Development Goals, in particular Goal 3, which aims to ensure healthy lives and promote wellbeing.[52] At a time of increasing costs of commercial medicines[53] and increasing gaps in health-care access,[54] the sustainable and equitable use of medicinal plants, particularly in the form of herbal medicines, could substantially contribute to this Goal.[13] Millions of people worldwide have restricted access to pharmaceutical drugs and rely on plant-based preparations as their primary or only source of medication.[13] The large role of medicinal plants in many people's lives was evident during the COVID-19 pandemic, during which vulnerable populations with restricted access to pharmaceutical medications and vaccines turned to herbal medicines.[55] However, the lack of fundamental research and evidence-based education on the safe and effective use of herbal medicines leaves their potential benefits for human societies largely unexplored and might lead to them becoming serious health risks instead.[56]

Beyond human health, medicinal plants can encourage national and global research and education programmes, contributing to the Education for Sustainable Development (Goal 4) by increasing awareness for safeguarding biodiversity through its sustainable use.[57] For example, there are at least 105 educational programmes in biodiversity and health interlinkages from 89 institutions in 30 globally distributed countries, primarily in the faculties of public health, veterinary sciences, and medicine.[58] Although not referring specifically to medicinal biodiversity, these numbers indicate that transdisciplinary research on medicinal plants within the planetary health framework (ie, linking ecosystems and human health) might be an important educational example emphasising the interdependence between humans and nature.

Transdisciplinary knowledge on medicinal biodiversity can be effectively transferred between research institutions and local and indigenous communities through educational programmes promoting sustainable management of local natural resources and disease prevention and ultimately establishing strong interconnectedness between research and education.[59] The bidirectional transfer of knowledge of medicinal biodiversity can provide fair and equitable sharing of the benefits of the use of local genetic resources, implemented through the Nagoya Protocol of the Convention on Biological Diversity.[60]

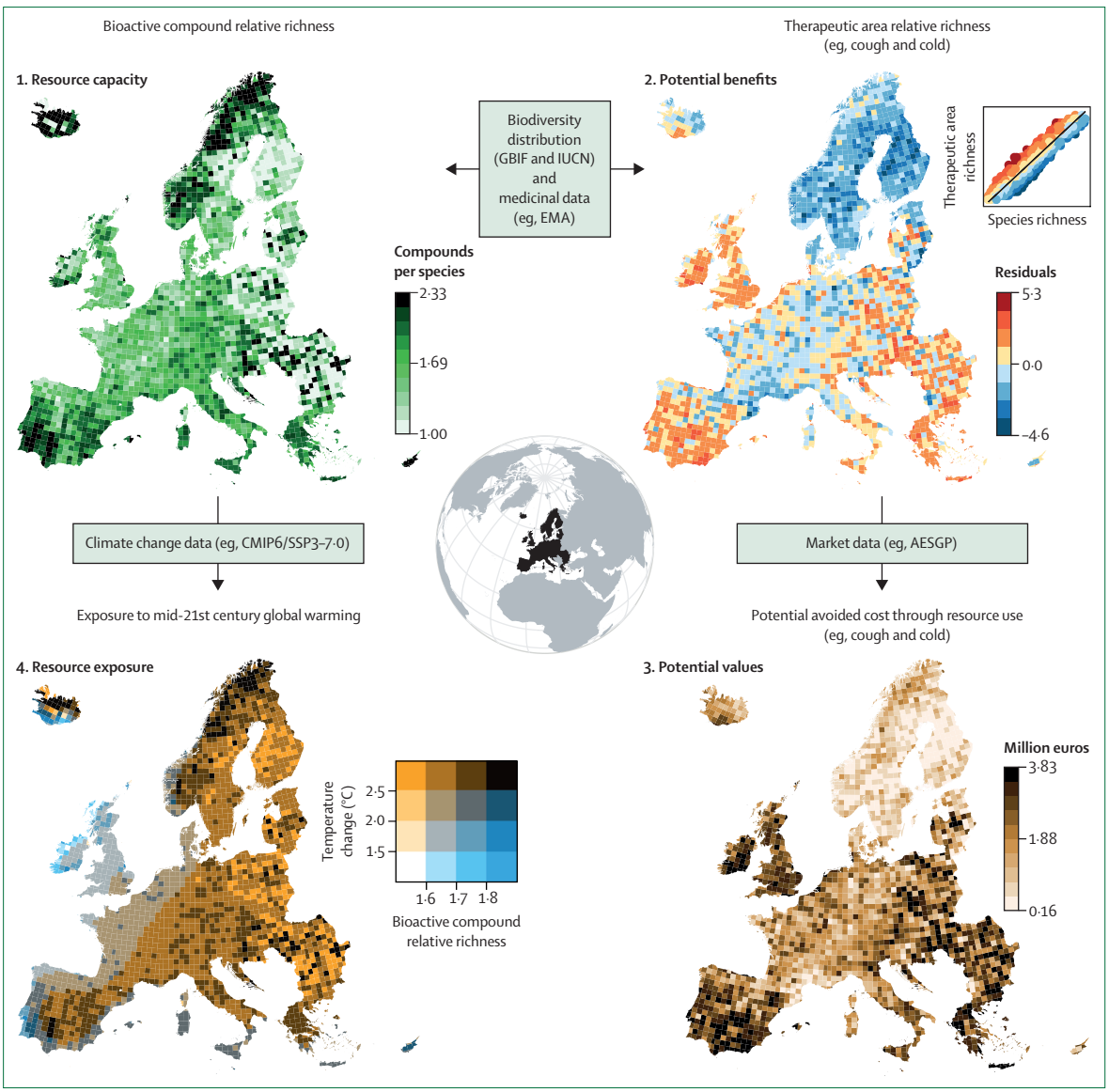

Figure 2: **Quantification of natural medicinal resources and their exposure to global environmental change**
Suggested analytical approach and required datasets for estimating the four proxy spatial indicators included in the evaluation of natural medicinal resources. These indicators are applied to the European Economic Area and associated countries (excluding overseas territories). Resource capacity is approximated by the mean number of pharmacologically relevant bioactive compounds per medicinal plant within a native species assemblage (ie, map grid cell). The potential societal benefits, with the use of resources, are approximated by the residuals of a linear regression between the total number of medical plants within an assemblage and the number of medicinal plants showing a particular therapeutic property (eg, treatment of cough and cold), with positive values indicating an excess and negative values indicating a deficit in the focal therapeutic benefit of the assemblage. Potential economic value is approximated by distributing the total annual expenditure on over-the-counter industrial medicines for a particular therapeutic area, weighted by the therapeutic area relative richness of each assemblage. The exposure of natural medicinal resources to global warming is approximated by overlaying annual temperature change on the map of bioactive compound relative richness. Temperature change is estimated by calculating the difference between a baseline period (eg, 1961–90) and mid-21st century (2040–69) under a future scenario of societal development (eg, SSP3–7·0). The proposed indicators can be starting points for further development of robust methodological approaches of the evaluation of medicinal plant resources. AESGP=Association of the European Self-Care Industry. CMIP=Coupled Model Intercomparison Project. EMA=European Medicines Agency. GBIF=Global Biodiversity Information Facility. IUCN=International Union for Conservation of Nature. SSP=Shared Socioeconomic Pathway.

Exposure of medicinal plants to global environmental change

The global environmental crisis in the anthropocene threatens all aspects of biodiversity from genes[61] to species[3] to ecosystems.[62] The effects of land-use change on biodiversity loss are jeopardising the long-term maintenance of ecosystem functions globally.[62] Furthermore, climate change has already increased species extinction risk and its effects reinforce those of land-use change, with predicted detrimental effects on biodiversity in future decades.[63] An increase of more than 2°C in annual temperature compared with pre-industrial levels

would substantially increase species extinction risk, with the geographical ranges of approximately a third of plant species predicted to contract by more than 50%,[64] causing serious disruptions to ecosystems globally. Being an integral part of terrestrial biodiversity, medicinal plants are also detrimentally affected by global environmental change,[9,10] yet comprehensive studies on the risk that extinction will pose to this crucial aspect of biodiversity are lacking.

See Online for appendix

For the **public biodiversity databases**, see https://www.gbif.org/, http://powo.science.kew.org, and https://www.iucnredlist.org/

Global warming, the associated temperature extremes and droughts, and the rise in atmospheric CO_2 concentration are also expected to affect the production of plant secondary metabolites. These abiotic factors are among the major drivers of plant phenological changes in the production and release of flavonoids, phenolic acids, and plant volatiles.[65] Although evidence of the consequences of these metabolic changes on plant fitness and adaptation is still lacking, changes in abundances of bioactive compounds could disrupt ecological processes, ecosystem functions, and their medicinal contributions to human societies.

Basic and transdisciplinary research to address the threats to medicinal plant resources because of global environmental change is of the utmost importance. Integrative approaches that combine diverse scientific principles, including climate science, satellite observations of the earth, and biodiversity genomics, have tremendous potential to predict the effects of global environmental change both in species extinction risk[66] and in the production of pharmacologically relevant bioactive compounds through adaptive changes in genes involved in biosynthetic pathways.

The geography of medicinal plant resources

Because of the importance and potential of medicinal plants in the contributions of nature to human societies, and threats to them because of increasing global change, we propose a set of spatial indicators that can approximate different attributes of medicinal plant resources and their exposure to alternative scenarios of future societal development (figure 2). The purpose of these indicators is to encourage further methodological development and transdisciplinary research on the multiple aspects of medicinal biodiversity and to highlight their potential contribution to planetary health.

Given the ongoing progress of the EU in the evaluation of herbal medicines, we show the application of these indicators in Europe. The Committee on Herbal Medicinal Products of the European Medicines Agency has so far evaluated 111 medicinal plant species that are native to Europe in the form of monographs.[19] These monographs represent scientific evaluations of safety and efficacy information about species and herbal products intended for medicinal use, including non-clinical and clinical data, and their documented long-term use in the EU. We reviewed these monographs and compiled a dataset containing the reported groups of relevant bioactive compounds and the approved therapeutic areas associated with each plant (appendix pp 3–10). This dataset is used as the evidence-based foundation for the proposed spatial indicators. We also retrieved information on species taxonomy and native geographical distributions from public biodiversity databases and created a spatial database that links species distributions to bioactive compounds and therapeutic areas.

Indicator 1: the capacity of medicinal plant resources

In our proposed framework, pharmacologically relevant bioactive compounds represent the capacity of ecosystems to provide medicinal resources and are acknowledged as species traits that are involved in fundamental ecological processes. We quantify this biochemical trait diversity as the mean number of bioactive compounds per species within a species assemblage (ie, map grid cell). The resulting map of bioactive compound relative richness can identify regions with substantial functional diversity indicative of richness in ecological processes, from increased biotic interactions in the Mediterranean biodiversity hotspot to adaptation to climate extremes in circumpolar Europe. This indicator also suggests that these regions might have increased capacity to contribute plant-based medicines for treating a substantial number of diseases (figure 1). Further research on the ecological roles of the bioactive compounds in medicinal plants and their underlying genetic variation will allow for the development of integrative, multidimensional indicators of ecosystem processes that can be used for monitoring ecosystem responses to environmental change, thus assisting the sustainable management and protection of natural medicinal resources.

Indicator 2: potential societal benefits of medicinal plant resources

The societal benefits of the sustainable and efficient use of medicinal biodiversity rely on robust, evidence-based knowledge of plant therapeutic properties. There is currently a small amount of this information, but it continues to increase. For the evaluated set of medicinal plants in this Personal View, several therapeutic areas have been approved by EMA (appendix pp 7–10). We propose the use of therapeutic area relative richness as a proxy indicator of the societal benefits of a medicinal species assemblage (figure 2). We quantify this indicator as the residual value of a regression between the total number of medicinal plants and the number of plants showing a particular therapeutic property (figure 2). This indicator highlights the excess (ie, positive values) or deficit (ie, negative values) of a species assemblage in its potential to treat a disease if these species are used as herbal medicines. The indicator can also identify regions that have substantial therapeutic potential and warrant

further bioactivity investigation, clinical investigation, and sustainable management prioritisation regarding the focal therapeutic area.

Indicator 3: potential economic values of medicinal plant resources

Inspired by the Avoided Cost Method of environmental economics,[67] we propose a spatial indicator that aims to evaluate the actual monetary cost of the non-use of medicinal biodiversity on society in the form of herbal medicines. We use the total annual expenditure on over-the-counter industrial medicines for a particular therapeutic area in Europe,[68] assuming a common economy, and distribute this total value according to the relative richness of the focal therapeutic area in each species assemblage (figure 2). This indicator approximates the cost that could be avoided by the consumer, as the major part of public and private expenditure would initially be allocated to clinical research on the safe and effective use of herbal preparations derived from the evaluated plant species assemblages. Although this monetary spatial indicator might underestimate the potentially avoided cost to the consumer, it shows that the establishment of herbal medicines as a cost-effective and accessible therapeutic source can substantially contribute to economic prosperity and constitute a sustainable, nature-based solution to global health care.

Indicator 4: the exposure of medicinal plant resources to global change

Using environmental change projections for the mid-21st century, we can assess the environmental exposure of medicinal plant resources in alternative scenarios of societal development, namely shared socioeconomic pathways, from sustainable land use and low warming to highly intensified land use, high emissions, and global warming.[69] In our application case, we calculated the difference in mean annual temperature between a baseline period (ie, 1961–90) and the mid-21st century (ie, 2040–69)[70] with a relatively high level of emissions (SSP3–7·0) and overlayed these changes on the map of bioactive compound relative richness. This exposure indicator can show reservoirs of bioactive compounds (ie, high resource capacity) that are exposed to high warming (figure 2). With the same approach, exposure to land-use change (eg, intensification of agriculture) with the same shared socioeconomic pathway can also be assessed.[61] Transdisciplinary research on the therapeutic properties and extinction risk of medicinal species will allow further development of crucial environmental change thresholds for assessing vulnerability of resource capacity.

Conclusion

In this Personal View, we outlined and integrated existing and emerging transdisciplinary knowledge to highlight the value and environmental exposure of medicinal plant resources as important components of the interface between biodiversity and human societies. We elucidated the multiple aspects of medicinal biodiversity, from its important part in maintaining ecological functions and healthy ecosystems to its potentially major contribution to human health and sustainable development, and propose the application of proxy spatial indicators to quantify these aspects. The sustainable and equitable use of medicinal plants would represent our cultural diversity and commonalities and their contributions beyond human health, involving multiple values of human societies (figure 1). We hope that our framework will encourage initiatives and transdisciplinary research funding schemes[66] to promote transformative change in planetary health and contribute to the Sustainable Development Agenda.

Contributors

This Personal View was conceptualised by ST and DN-B. Formal analysis was done by ST and visualisation was done by ST and EGD. The original draft was written by ST and EGD. The original manuscript was revised by all authors.

Declaration of interests

We declare no competing interests.

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