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Biodiversity: the overseen source of human health

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Abstract

Biodiversity is the measure of variation of life in a given ecological system. Biodiversity provides ecosystems with the robustness, stability and resilience that sustains them. This is ultimately essential for our survival, as we depend on the services that natural ecosystems provide us (food, fresh water, air, climate, and medicine). Despite this, human activity is driving an unprecedented rate of biodiversity decline, which may jeopardise the planet's life support systems if no urgent actions are taken. In this article, we show why biodiversity is essential for human health. We raise our case and focus on the biomedicine services that are enabled by biodiversity and present known and novel approaches to promote biodiversity conservation.

The current state of biodiversity

The SARS-CoV-2 pandemic brought an unprecedented global human health crisis that has highlighted the interdependence of human and planet health. The pandemic highlighted the need for a clear view of the intricate interconnections between human health, biodiversity and planetary health, which ultimately rely on a delicate balance of natural systems and the wise use of natural resources.

Biodiversity is the variety and variability of life on earth and is typically measured by variation observed at the genetic, species and/or ecosystem levels [1, 2]. Biodiversity sustains life on earth and its conservation is imperative for the survival of all species, especially ours. Biodiversity sustains the robustness, stability and resilience of ecosystems [3] that provide essential services for our wellbeing, such as fresh water, pollination, soil fertility, food and medicine [4, 5]. Biodiverse ecosystems are more resilient to the effects of climate change and could attenuate its effects as well as promote climate adaptation through their influence on the carbon, nitrogen and water cycles [3]. The impact of biodiversity can be appreciated even more by considering the role of the microbiome in all earthbound species (including us). The human microbiome is a complex collection of symbiotic microbes found in most body parts – with distinctive signatures [6]. Our microbiome represents a virtual organ that performs essential body functions (e.g., digestion and synthesis of essential nutrients), that maintain our homeostasis [7-9] and importantly, it educates our immune system and modulates our immune responses [10]. Our microbiome is therefore intrinsic to our well-being, in such a way that we are now (together) considered as a single ecological unit: “the holobiont” [4, 11]. A healthy microbiome is a diverse microbiome, and microbiome richness and diversity is highly influenced by the environmental biodiversity of our dwellings and surroundings [12]. This was demonstrated by studies comparing the diversity of urban vs rural societies where humans residing in rural societies were found to harbour microbiomes with higher species richness [13]

The trend in biodiversity decline parallels the increased incidence of chronic inflammatory diseases such as allergic and autoimmune conditions [14]. To date, multiple research studies have associated biodiversity decline and an increased risks of chronic and inflammatory diseases via microbiome diversity. Lower microbial diversity in urban areas limits the colonisation of our microbiome by environmental microbes – a key determinant of microbiome diversity [15, 16]. This alters the microbial communities inhabiting our microbiomes, in a way that it impairs the training of our immune system, increasing the odds of developing aberrant inflammatory responses [17]. For example, a recent study of the prevalence of atopy in children living in urban vs rural environments. This study found that atopy was less frequent in children exposed to more biodiverse environments. The skin microbiota of these children had a higher diversity of gammaproteobacteria, a bacterial taxon known to produce IL-10 - an important anti-inflammatory cytokine that mediates immune tolerance [18]. It is thus foreseeable that biodiversity loss will lead to an increase in human allergic and autoimmune conditions and

have detrimental consequences on public health in general. This makes the loss of biodiversity an acute public health problem.

Despite its essential character, human activity has pervasively affected biodiversity and the global climate. The 2019 Global Assessment Report from the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPEBS), highlighted an unprecedented, accelerating rate of species extinction (10,000-100,000 species per annum[i]. Here, it is shown that one of the eight million known animal and plant species are currently threatened. It also revealed that approximately 75% of land-based and 66% of marine global ecosystems have been altered into less productive land (majorly for crop or cattle raising). This has caused an overall 22% loss of global land productivity. Furthermore, the accelerated rise of the global temperature (>1^{o}C relative to pre-industrial times) mainly driven by anthropogenic carbon emissions have raised sea levels, eroding coastal habitats that protect 100-300 million people against floods and detrimental hurricane effects [19].

It is now evident that the dramatic impact of human activity upon biodiversity negatively feeds-back on people themselves as well as on animals and on the environment. As a case in point, the World Health Organization (WHO) has established the 'One Health' approach that involves different sectors and disciplines to balance and optimize health at the global level, referring to plants, ecosystems, animals, and human[ii] [20]. To this end, governments, researchers and specialised workers are implementing shared databases and surveillance across different sectors that ultimately serve to establish joint responses to health threats [21].

Transformative policies to protect biodiversity are urgently needed. The IPEBS Global Assessment report states that current conservation efforts are insufficient for achieving the UN sustainable development goals. The Convention on Biological Diversity established twenty biodiversity targets to be met in 2020[iii] [22]. These were mostly unmet. The current rates of biodiversity and ecosystem decline will jeopardise the planet's life support systems and undermines our ability to meet the targets of the UN Sustainable Development Goals related to health, nutrition, water and land, and the economy [19, 23]. Current models project a global biodiversity decline comparable to the loss of all species in up to 8 million km^2 of pristine habitat by 2050, which could possibly have slower decline rates if we adopt sustainability policies [24].

In this article, we demonstrate that the survival of our species is highly dependent on the *in situ* conservation of biodiversity (beyond the preservation of species and compounds in isolated

archives). We also describe some existing and proposed methods for biodiversity conservation.

Biodiversity as a medicinal source

Biodiversity as a source of natural medicinal compounds

The use of nature-derived products for medicinal purposes has supported the development of pharmaceutical products since ancient times [25]. It is estimated that approximately 7% (26,000) of known vascular plant species have been used for medicinal purposes [26]. Globally, over 30% of new drugs derive from natural molecules sourced from plants and microbes identified by science and/or through indigenous knowledge. For instance, over 70% of cancer therapeutics derive from existing natural compounds [27]. Currently, the majority of pharmacologically active agents in modern medicines are synthesised from templates provided by existing natural compounds (Box 1) and many new medicines are still sourced from nature [27, 28]. Namely, over the last 50 years, over 30,000 new compounds and over 300 filed patents correspond to those sourced from marine species [29].

Box 1. Biodiversity for future discoveries – the case of Paclitaxel

Paclitaxel, a chemotherapeutic essential for treatment of breast, ovarian and lung cancers, is an excellent example of the relevance of biodiversity conservation to safeguard future drug discovery. Paclitaxel is a product of a two-decade research collaboration between the National Cancer Institute and the US Department of Agriculture, which screened 115,000 extracts from 15,000 plant species for natural anticancer metabolites. The compound, Taxol, was isolated from the bark of the Pacific yew tree *(Taxus brevifolia*). While Taxol was initially disregarded as a promising compound, a decade after its isolation its antitumour efficacy was proven in murine models, which prompted clinical trials and later approval for breast cancer treatment [30]. However, the production and use of Taxol came at great expense for the species. The removal of the Taxol bark kills the slow-growing tree and, Taxol populations have declined significantly due to overharvesting and the species is now listed in the IUCN Red list of threatened species[iv] .This raised a conflict regarding the unsustainable overharvesting of Taxol and demand for it as an essential cancer drug and prompted the search for alternatives. In 1993 Taxol was found on an endophytic fungus, *Taxomyces andreanae,* isolated from the inner bark

of the taxol producing plant [31]. This finding prompted the search for taxol in other fungal species and in 1996, Strobel et al. found that Taxol was produced by several unrelated species of fungi (e.g., *Alternaria sp.*, *Fusarium lateritium*, *Monochaetia sp.*) [32]. These discoveries prompted scientists to question whether bioactive metabolites such as taxol are produced by microbial symbionts, rather than their host [33]. The role of the many microbial species are still unknown to us, as is the potential drugs they may give rise to. At present, the advent of high throughput sequencing technologies has enabled a more accessible study of the microbes that inhabit the planet, and multiple projects mapping them throughout the world are ongoing [34]. The growth and/or engineering of microbes for the production of biomolecules has progressed exponentially in the last two decades and could someday solve the overharvesting of species [35]. Taxol exemplifies the importance of biodiversity conservation, showing that even the most miniscule lifeforms can provide invaluable biomedicinal compounds.

The most well-known examples of pharmacological agents derived from natural sources are caffeine, acetylsalicylic acid (aspirin) and the plant-derived antimalarial agents, quinine and artemisinin. Quinine is extracted from the bark of the South American *Cinchona sp.* trees. Quinine is still the preferred treatment for chloroquine-resistant malaria caused by *Plasmodium vivax*, pregnant women (during the first trimester of pregnancy) and severe cases when other treatment options are not available [36]. The synthetic production of quinine and its derivatives [37, 38] has preceded the loss of value and the traditional knowledge about the Cinchona tree. For example, in Peru (where 20 out of the 29 Cinchona species originate), the traditional knowledge enabling the recognition and differentiation of Cinchona species has been lost and many of the species are under threat of extinction[v]. It is hoped that recent discoveries of the potential of other Cinchona alkaloids, such as optochin, which possesses highly selective and potent antibiotic activity, may revive interest in Cinchona conservation [39].

Artemisinin is sourced from the leaves of the Chinese sweet wormwood plant (*Artemisia annua*) and has been a traditional antimalarial remedy in China for >2000 years. Artemisin gained international interest since the early 1970's and has been adopted globally as an essential component of antimalarial combination therapies. Despite recent breakthroughs on its partial production using heterologous microbes [40], the synthetic production of artemisinin in a cost-effective manner has not yet been fully achieved [41]. Thus, the production of Artemisin still relies on the extraction of the molecules from cultivated *Artemisia sp.* plants [42] that are also the source for numerous bioactive compounds (terpenoids, saponins, flavonoids) with

potential application for the treatment of several other diseases, such as cancer, inflammation and viral infection [43, 44], emphasising the need for their conservation [45].

Likewise, soil fungi has been the source for discovery of most known antibiotics (e.g., streptomycin, penicillin) and antifungal agents (e.g., griseofulvin) [46]. Thus their conservation is essential for the discovery and development of antimicrobial therapies that may tackle the ongoing global antimicrobial resistance crisis [47].

Biodiversity conservation is essential for drug discovery and development, as its loss eliminates yet unidentified genetic and natural chemical resources [25], and to date, only a small fraction of all known species have been studied for pharmacological potential [48]. It is estimated that the decline in biodiversity has driven the loss of a potentially important drug every two years [49] and threatened the loss of 21% (~15,000) species of known medicinal plants [28, 50]. Biodiversity sustains the complex interdependent relationships between species (many of which are still unknown). For example, the endangered cassowary (*Casuarius sp.*) consumes and disperses the seeds of 238 species of plants [51]. Just as the extinction of the cassowary may threaten the existence of some of the plant seeds it disperses, the disappearance of species whose ecological functions remain unknown may lead to the loss of other species, ultimately reducing the number of unidentified potential medicinal molecules.

Traditional (indigenous) knowledge and molecular medicine

An estimated 4 billion people rely on natural medicines for their basic healthcare needs [52]. Although more prevalent in lower-income countries, recently a worldwide increase in interest and adoption of natural medicines has been made evident by the increase in export of medicinal plants [53, 54]. This can be attributed to a public need for affordable remedies, and the perception that "natural" products are safer and more effective [55]. In 2003, the World Health Organisation (WHO) estimated an annual global market size of USD 60 billion, by 2012 the global size of traditional Chinese medicine was USD 83 billion[56]. In 2021, the annual global market size for herbal medicines was USD 166 billion and is projected to grow to USD 348 billion by 2028[vi].

Indigenous knowledge plays a critical role in the discovery of molecules for medicinal applications. Indigenous people have tested the use of these molecules for extensive purposes, through observation and empirical experimentation. Consequently, they have developed a unique understanding of natural extracts and their effects on their well-being, cultivating a close connection with the ecosystems and biodiversity that surrounds them. This unique

connection allowed indigenous people to establish innovation and knowledge systems and practices that sustainably use and manage the molecular biodiversity found in diverse ecosystems[53]. This indigenous knowledge has been a rich source inspiring modern drug development for decades [55]. However, globalisation has caused a fast decline of traditional medicinal knowledge, as it undermines local rural traditions and changes farming practices. It is now evident that traditional farming systems and the diversity of medicinal plants are directly correlated.

The loss of traditional knowledge threatens the potential to identify new medicines [57]. Revisiting indigenous knowledge through ethical engagements offers rich opportunities for sourcing novel medicines. Indigenous knowledge is an undervalued form of intellectual property and receives little or no recognition. Indigenous knowledge often lacks enforceable legal frameworks, thus the rights of indigenous peoples as custodians of this knowledge are often neglected and requires change [58].

Biodiversity is essential in disease prevention and treatment

More species means less human disease. This is not only true due to potent, robust medications being identified and produced from endemic plants, animals and fungi, but also because studies indicate that in fact biodiversity loss increases disease transmission [59]. The SARS-CoV-2 pandemic is a good wake-up call that many communicable and other diseases could be prevented and treated by safeguarding global biodiversity, because as expanded below biodiversity conservation is crucial for the prevention of zoonotic diseases (such as COVID19) and for the development of treatments or interventions (For example the blood of the endangered Atlantic horseshoe crab (*Limulus polyphemus*[vii]) was critical for the development of COVID vaccines) [60]. The relevance of biodiversity to biomedicine is discussed here through the next two cases: cancer resistance and communicable diseases.

Biomedicine for the reversal of resistance in cancer

One of the main challenges in cancer therapeutics is the development of drug resistance. Mechanisms of drug resistance include elimination of drugs by membrane transporters, DNA damage repair, resistance to apoptosis, detoxification and drug inactivation, drug target alterations, epigenetic changes, and epithelial to mesenchymal transition [61]. Cancer cells can either be intrinsically resistant to chemotherapeutics or develop resistance after drug exposure. Various natural products have been shown to reverse drug resistance by diverse mechanisms

and are therefore excellent candidates for further exploration in the treatment of drug resistance [62].

Many natural compounds are fourth-generation inhibitors of the most studied ATP-Binding Cassette (ABC) transporters, such as P-glycoprotein 1 also known as multidrug resistance protein 1 (MDR1) which is crucial for the development of resistance to multiple chemotherapeutics [63, 64]. For example, quercetin, resveratrol and catechins have been shown to inhibit MDR1 and reverse Adriamycin resistance in chronic myeloid leukaemia cells [65]. Efferth and colleagues tested purified compounds widely used in Chinese traditional medicine and identified their effects. Notably, Artesunate derived from *Artemisia annua* or sweet wormwood and bufalin, a bufotoxin from the Asian toad (*Bufo gargarizans* and *Bufo melanostictus)* venom showed antileukemic activity as single agents and increased daunorubicin accumulation in multidrug resistance-associated protein-1 (MRP1)-expressing cells [66]. Similarly, epigallocatechin gallate, a green tea (*Camellia sinensis*) polyphenol, increased sensitivity to vincristine in resistant epidermoid carcinoma cells by increasing intracellular vincristine concentration [67]. Matrine, an alkaloid derived from *Sophora flavescens*, reduced protein levels of MDR1 in sarcoma cells [68].

Another promising strategy to overcome drug resistance is that of apoptotic and non-apoptotic cell death. To date there are several herbal compounds that act synergistically with radiation and chemotherapy by inducing apoptosis and autophagy. These include alkaloids (berberine, noscapine, melatonin, piperlongumine), diarylheptanoids (curcumin), flavonoids (luteolin, naringenin, quercetin, silibinin), phenolic compounds (caffeic acid, emodin), phytosteroids (polyphyllin D), stilbenoids (resveratrol) [61, 69].

A good example of a multitargeted biopharmaceutical is Shikonin. Shikonin is a natural naphthoquinone component with antioxidant and anti-tumour function. It is a major component of a Chinese herbal medicine zicao, the dried root of *Lithospermum erythrorhizon* also known as purple gromwell. Shikonin suppresses hepatocellular carcinoma (HCC) proliferation and epithelial mesenchymal transition and accelerates cell death of HCC [70]. Additionally, it induces necrosis in the cells that overexpress multi-drug resistance anti-apoptotic proteins. Shikonin down-regulates surface expression of CCR5, a primary HIV-1 coreceptor, on macrophages, inhibits the replication of the HIV in monocytes/macrophages and inhibits replication of a multidrug-resistant HIV strain. The anti-HIV and anti-inflammatory activities of Shikonin may be related to its interference with chemokine receptor expression and function [71].

Together, these studies reveal the importance of using natural substances in cancer treatment as an approach to overcome drug resistance [72]. Natural products can target multiple signalling pathways and processes in cancer cells. Due to the development of resistance to classic chemotherapy as well as new targeted therapies, natural products, considered as multi-targeting drugs, should be of interest to future cancer research. More human clinical trials are needed to further elucidate the potential use of natural products in overcoming drug resistance and protection of the natural repository should be a priority in cancer research (Box 2).

Box 2. Novel antibiotics and cancer treatments: elasmobranchs in human health

Elasmobranchs are a subclass of cartilaginous fish species (Class Chondrichthyes) that includes sharks, skates, rays, guitarfish, and sawfish. Elasmobranchs diverged from the main line of vertebrate evolution 400 million years ago, continuing to be successful in oceans and seas around the world. It's almost impossible to find a "sick" shark or ray in the wild due to their uncanny ability to remain healthy, though they are now facing a "mass extinction" because of extractive human activities, mainly overfishing. Recurring observations of infection-free healing of wounds among elasmobranchs have oriented scientific research toward exploring them as sources for novel antibiotics. In 1993, Squalamine, an aminosterol with broad antifungal, antibacterial, and antiprotozoal activity, was isolated from the spiny dogfish (*Squalus acanthias*) stomach [73]. Squalamine has also been found to be antiangiogenic, inhibiting the growth of solid tumours by limiting their blood supply. Furthermore, Squalamine shows tremendous promise for treatment of Parkinson's disease and human weight control.

Basic understanding of the elasmobranch immune system has received considerable attention since the early work of comparative immunology pioneers Marchalonis and Edelman, who paved the way to this field [74]. Elasmobranchs are the earliest jawed vertebrates to possess all the components necessary to perform the specific responses associated with adaptive immunity [75]. One particularly exciting approach is based on the unique structural properties of some of the elasmobranch immunoglobulins. Existing traditional monoclonal antibody therapeutic approaches are limited by the large size of these molecules. These limitations could be overcome with Immunoglobulin new antigen receptors (IgNAR), which are unique single domain antibodies found in sharks [76]. These are considerably smaller (~12 KDa vs ~150 KDa) than traditional monoclonal antibodies, and thus are referred to as 'nanobodies'. Their significantly smaller size carries the advantage of diminishing steric hindrance that might prevent larger antibodies from accessing and recognizing certain epitopes.

Biomedical applications of elasmobranch research are starting to receive favourable attention with advances in the understanding of elasmobranch physiology, especially the immune system. Recent advances are leading to the development of new genomic tools, and discovery of novel antimicrobials and compounds produced by unique immune tissues of elasmobranchs. Even though translation of this knowledge to clinical therapies remains a challenge, all the related genomic tools, novel antibiotics and antibiotic structures cannot be applied to patients if the source organisms are allowed to go extinct.

Conservation and Biodiversity Preservation for the Maintenance of Global Health due to Emerging infectious diseases

Emerging infectious diseases (EIDs) constitute a new global threat to public health. The SARS-CoV-2 pandemic raised multiple questions regarding the relationship between humans, the environment, and other species. Could the pandemic have been prevented by adequately preserving wildlife habitat? Did close contact and consumption of the wild species lead to the pandemic?

Three hundred and thirty-five EIDs appeared between the years 1940 and 2004. Three out of every four new or emerging infectious diseases are zoonotic, with 72% of these zoonoses caused by wildlife pathogens [77]. Zoonosis outbreaks have been increasing globally in both number and richness since 1980 [78]. Besides SARS-CoV-2, most recent examples of zoonoses that significantly impacted public health on a global scale include SARS-CoV, MERS-CoV, Zika and Monkeypox [79, 80].

Degradation of ecosystems due to human activity (such as agriculture, road building, mining and others) is the primary driver of EIDs and zoonosis outbreaks. Forest fragmentation and biodiversity loss are linked to the increased risk of Lyme disease in the US, while agricultural expansion is associated with Nipah virus spread in Malaysia [81]. Ebola viruses are zoonotic pathogens, whose infection leads to a 40-90% human fatality rate. Although human outbreaks are linked to infected great apes and duikers, these are not the natural viral hosts as evidenced by their high mortality rates. Recent studies suggest that bats are putative reservoir hosts and play a major role in the viral transmission cycle [82]. A higher exposure to animal reservoirs, likely displaced from their habitats as a product of human interventions (hunting, agriculture, housing), contributes to the recurrence of Ebola outbreaks (13 outbreaks in the last 10 years) [83]. The high fatality rates (ranging from 51 to 83%) and frequency of viral recurrence, urges

an improvement of the current outbreak prevention strategies, ideally incorporating the One Health philosophy [84].

Jones and colleagues demonstrated that human population density predicts EID events, supporting the hypothesis that disease emergence is directly linked to human urban development In this study, human population density, growth, and latitude were found to be key predictors of the emergence of zoonotic EIDs [77]. In a recent study, Jones and colleagues found key evidence explaining why the decrease in biodiversity increases the risk to EIDs. After analysing data from 6801 ecological sites worldwide, it was found that sites with substantial human activity (e.g., agriculture, urbanisation), had a higher proportion (up to 72%) of species that are known to be wildlife hosts of human-shared pathogens. In these ecosystems, the loss of species opens niches that are often filled by species that tend to be hosts for zoonotic pathogens. For example, these ecosystems are more likely to harbour mammals that are hosts for a high number of pathogens (e.g. rodents, and bats) [85].

This work calls for a global health maintenance plan that promotes the conservation of biodiversity rich areas, and oversees human activity and population growth, in order to minimise their impact on biodiversity [77]. In response to these findings, the IPBES produced a comprehensive workshop and report on Biodiversity and Pandemics. This report calls for the shift from pandemic control to pandemic prevention via holistic management of rural frontiers and wildlife trade restriction. The authors suggested the launch of a high-level intergovernmental council on pandemic prevention implementing the One Health philosophy, which connects human, animal and environmental health [86]. In support of this IPBES pandemic prevention plan, a group of expert biologists and economists published an “Ecology and economics for pandemic prevention” report, which estimates that the deforestation control, wildlife trade cessation, and epidemiologic efforts to prevent pandemics would cost 22-33 billion USD per annum, which is by far less than the 5.6-trillion USD lost due to the COVID-19 pandemic [87].

Biodiversity Preservation via Biomedicine: Modern Solutions

Linking traditional and modern pharmacy: biodiversity conservation via further exploration of biodiversity

The value of biodiversity can be quantified by the value of the services/products it provides (125 trillion USD per annum in 2011) [88, 89]. For example, its value can be framed in terms

of the potential products for agricultural, industrial and pharmaceutical use that can be sourced from the species harboured by an ecosystem [90, 91]. To date, biodiversity is still the main source of pharmacologically active biomolecules enabling drug discovery and thus, the development of new medications for disease prevention and control [27, 92, 93]. In fact, recent reports show that up to 70% of all small molecule drugs approved by the FDA between 1981-2014 were sourced from or were inspired by nature [94, 95]. Most of these molecules were sourced from medicinal plants which in 2015 reported a global trade value exceeding 2.5 billion USD [96]. Similarly, other reports estimate that marine ecosystems can be attributed a worth of 563 billion–5.69 trillion USD for potential (yet to be discovered) anti-cancer drugs [97]. Furthermore, the loss of species with medicinal products will also deprive other animals from their medicinal benefits. Other animals also use plants, insects and other inorganic materials for self-medication. For example, apes have been observed to select sections of medicinal plants by taking off leaves, breaking stems and sucking their juice to alleviate pain or treat certain ailments. Self-medication in wild animals is believed to be a behavioural adaptation evolved primarily against parasites and associated diseases (zoopharmacognosy) [98]. Given that parasites are often intermediary hosts for pathogens [96], this prompts us to question the potential impact that these may have on the emergence of zoonotic diseases. Furthermore, zoopharmacognosy has been a source for traditional knowledge for drug discovery that is still valid. For example, it has been recently found that certain plants used by animals also possess tumoricidal capacity [99].

Medicinal plant conservation and cultivation for biodiversity preservation

New biomedical technologies have advanced the discovery of new plant biomolecules for medical use. Yet, the exploration of potential medicinal plant species is insufficient, given the current biodiversity loss rates. At the same time, many of the known medicinal plant species are threatened due to over-exploitation. The wilderness or wildlands are the main source of medicinal plants [100, 101]. These natural areas are exponentially pressured and threatened by human activities, directly through activities such as agriculture, deforestation and logging; and indirectly by the detrimental effects of climate change on natural ecosystems [102, 103].

Although most medicinal plants are sourced from lower-income countries, these are shipped and marketed in high-income countries, which hold the majority of the trading markets [54, 55]. As of 1985, a surprising 18.9 percent (4,941 of 26,092) of the native plant species in China were used as drugs for traditional medicine [104]. In 2006, the WHO listed 21,000 medicinal

species [52, 105] and in 2021, The Royal Botanical Gardens Medicinal Plant Names Services (MPNS) identified 34,408 plant species that are currently used for medicinal purposes[viii]. The volume of medicinal plant harvested from the wild has been growing at alarming rates, with an 8–15 % annual increase of demands in Europe, North America, and Asia. These species are often overharvested to meet these demands, which jeopardises the species by reducing their abundance to a threshold at which their reproductive capacity becomes irreversibly damaged.

The conservation of medicinal plants can be achieved through several proposed methods, either *in situ* or *ex situ*. *In situ* conservation focuses on the on-site conservation of genetic resources on their natural habitats by establishing protected areas that safeguard them. This strategy maintains the conditions ensuring the genetic diversity, evolution, and adaptation of a species. It also safeguards the production of metabolites that are produced as a response to stimuli from their natural environment, which is the case for many medicinal products. *Ex situ* conservation involves the relocation of the species from their natural habitats to an area equipped for their protection (e.g., botanical gardens, seed banks) and/or their cultivation under controlled conditions. This approach sustains species which have high market demands, as it ensures that the medicinal compounds are produced to meet the market's demands and ensures propagation [103]. However, the cultivation of the medicinal plants may have negative implications, such as the reduction of the incentives to preserve native ecosystems [106]. The safeguarding of medicinal plants requires holistic conservation programs [103], integrating *in situ* and *ex situ* conservation practices, that include their domestication, breeding and selection [107]. These conservation programmes should be informed by research of local ecosystems and involve local populations, ensuring the conservation of traditional knowledge [108]. In addition, these conservation programmes should also be accompanied by researcher ensuring the efficient and sustainable production of plants' biomolecules, which may include biotechnological approaches improving yield and potency [109].

These conservation programmes should receive support from all stakeholders involved in the healthcare systems (Governments, the private sector, and the public). Biodiversity conservation is critical for the sustainability of our healthcare systems without which we cannot meet the demand of interventions (e.g., medicines, treatments, vaccines) required for the treatment or prevention of current and future threats to our health [92, 110]. It is evident that healthcare industries, and in particular the pharmaceutical industry, benefits from biodiversity derived products, particularly medicinal plants, which are a source of up to 80% of all registered medicines to date[ix] [111]. Surprisingly, despite the cumulative evidence highlighting the risks

that diversity decline imposes to their business models, pharma remains mainly uninvolved in biodiversity conservation. It has been proposed that if pharmaceutical companies invested 1% of their global spending into land restauration from now until 2050, 386 million hectares of valuable biomes could be restored. If this is achieved, pharma companies could then reap the benefits of a USD 30 trillion increase in global biodiversity services [112]. With this, we wish to remind public and private health care systems, the pharmaceutical industry and healthcare investors that biodiversity is a fundamental component of long-term business success, and its loss is a high risk to the sustainability of the industry. Thus, investing in biodiversity conservations, is investing in the long term success of the industry. Furthermore, in light of the upcoming COP-15 negotiation of the Nagoya protocol[x], we urge players of this sector to ensure the equitable sharing of benefits from drug discovery, in order to safe-guard the open access to these genetic resources.

Synthetic biology for biodiversity preservation

Synthetic biology is the science of engineering living organisms through genetic manipulation and construction of genetic circuits [113-115]. Synthetic biology may provide answers to multiple environmental challenges, such as climate change, scarcity of clean water, pollution [116], and medicine [117-119] with new means to produce living and non-living drugs with potentially positive impacts on biodiversity [120]. By reducing the time, cost and complexity of developing drugs, fuels, or raw materials, the field represents opportunities for a range of industries from agriculture to pharmaceutical. Some genetically modified crops have sustained livelihood and conservation benefits. For example, genetically modified cotton produces its own pesticide reducing pest damage in developing countries [120]. In 2006, a yeast strain that produces the precursor of artemisinin, an antimalarial drug was engineered [121]. Before this, artemisinin was extracted from *Artemisia annua*, which was in short supply and unaffordable. Re-engineering organisms to produce novel antibiotics and using modern gene-editing techniques such as the CRISPR/Cas9 gene editing system are providing novel approaches to combat bacterial resistance [122, 123]. Given the rapid evolution of bioengineering, synthetic biology represents a valid way to synergize with traditional knowledge, zoopharmacognosy, and natural medicinal product development to provide promising results for hard-to-treat diseases.

Concluding remarks

Biodiversity for biomedicine strongly relies on the balance of three main factors: the preservation of thousands of different species that populate the earth, the rescue of the ones faced with extinction, and the development of methods and technologies that allow extraction of biological/pharmaceutical compounds without harming existing ecosystems. It is dramatically clear that our society relies deeply on the earth's biological resources, but we also cannot afford to deplete them. A sustainable and circular bioeconomy considers not only the health and needs of the living generations, but also future generations (Box 3).

The variety of life on earth depends on species living together and depending on one another. Every living thing, including man, is involved in these complex networks of interdependent relationships and these ecosystems provide raw materials and resources for medicines that return to humans. Our future will not be sustainable without these "ecosystem services", or the so-called: natural capital. Extinction of one species could result in a domino effect disturbing the balance of many other species and subsequently affecting the health and prosperity of *Homo sapiens*. Losing one species could mean shutting down an entire "laboratory" that could hold the secret of a specific treatment tackling human disease. Now is the time to find ways and solutions to tackle the biodiversity loss by identifying novel, modern solutions to the problem.

Just as humans are holobionts – inseparable from their microbiome ecosystem, our planet can be considered a holobiont, encompassing all macro and micro- species living in a symbiotic association within biomes of the planet's biosphere [124]. Historically, conservations efforts have focused on the conservation of single "flagship" species, such as tigers, rhinos and pandas; which more easily capture the public attention, attracting efforts and funding. An approach that has been essential for the conservation of critically endangered species and also benefiting the habitats of these species. Despite these benefits, this conservation strategy can bias conservation efforts and often overlooks species that perform key functions for the maintenance of the habitat as a whole (e.g. pollinators and other insects, mycorrhizae soil fungi)[xi]. Based on palaeobiological evidence, a recent study showed that ecosystems with high functional richness and diversity are more resilient and persistent and demonstrate actions towards ensuring ecosystem functioning endure longer than those oriented towards the protection of taxonomic units [125, 126]. This revealed a marked decoupling between taxonomic and ecological turnover and as a conclusion encourages the adoption of conservation strategies that preserve the function of ecosystems and their services to humanity over those aiming for species preservation, as these are more long-lasting [126, 127]. Notably,

there is a gap between both conservation priorities and while their requirements may not always be complimentary [128], supporters for both strategies, agree that any conservation strategy should involve indigenous communities, whose deep connection with local biodiversity has proven essential to safeguard their surrounding ecosystems and will be essential to resolve the current biodiversity decline crisis [129]. It is our vision that the realisation of a holistic – One Health approach – will require the development of sustainable biodiversity conservation policies, with clearly defined targets, that incorporate a balance of both species and functional conservation priorities. But importantly their development must involve local, indigenous people, in a manner that it acknowledges their traditions and empowers their cultural heritage (See outstanding questions).

Box 3 - Perspective: Bioeconomy as a new means to sustain biodiversity?

Bioeconomy is a recent concept towards creating new economic strategies for sustainability and is defined by the European Commission (EC) as "the production of renewable biological resources and the conversion of these resources and waste streams into value added products, such as food, feed, bio-based products and bioenergy" [130]. Bioeconomy walks hand-to hand with sustainability that is, to utilise the existing resources in a responsible manner [131]. Sustainability is particularly important today as it is a balancing act between many dynamically changing factors of a growing human population and its demands, the changing physical environment, an ever-increasing waste that results from human activity, as well as related issues such as unjust land use[132]. Sustainable bioeconomy, therefore, promises to be a valuable tool in achieving the sustainable development goals (SDGs), since it can contribute to many aspects of SDGs such as food security and water availability (SDG-1, 2 and 6), climate change (SDG-13), job creation (SDGs1, 5, 8, 10) and sustainable consumption (SDG-9, 11, 12), as well as other SDGs [131].

Novel technologies can aid bioeconomy practices. For example, biotechnology and synthetic biology offer new avenues for the manipulation of biosynthetic pathways, production of natural compounds or their improved versions, and for micropropagation of many plant species so as to counterbalance the damaging effects of foraging from the wild (hence damaging effects on biodiversity) [133]. Of note, the EU definition of bioeconomy does not include biopharmaceuticals, as by-products and waste material from processes are not recycled in a

"cradle-to-cradle" approach of circular economy. This calls for an action to improve practices that align to the concept and scope of biodiversity.

The circular economy refers to continual reutilization of renewable resources while producing as little waste as possible, contributing to resource-efficiency. The bioeconomy and the circular economy could together steer sustainability using innovative technologies. Importantly, despite logistic culprits, many countries have eventually adopted strategies of circular economy in their agendas [133].

Clinicians corner

- Biodiversity is essential for drug discovery, as is the main source of inspiration for the development of treatments and interventions for current and future health threats.
- Biodiversity is essential for the control of zoonotic infectious diseases. Habitat loss displaces species and increases contact between human and animals that may harbour shared pathogens.
- To safeguard our health and the health of our planet, we need to take a One health approach, integrating balanced and sustainable conservation strategies aiming at protecting species and ecosystems. Importantly, this must involve local inhabitants, so that their knowledge and traditions are also safeguarded.
- Given the relevance to our health systems, efforts for biodiversity conservation should be a priority for the sector, including government agencies, NGOs and the private health industry, especially by the pharmaceutical industry.

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Declaration of interests

None are declared.

Resources

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