Global Partnership for Biodiversity, Medicine and Health

1. The importance of biodiversity for medicine

The diversity of life on earth has been a critical driver of biomedical discovery. Over half (593 of 1130) of the drugs approved between 1981 and 2010 were derived from natural products[1] – that is, from molecular entities produced by living organisms, such as mammals, fungi, bacteria, marine organisms, and especially plants. The focus of the Global Partnership for Biodiversity, Medicine and Health is to accelerate the discovery and development of new medicines derived in particular from the huge diversity of plant, fungal, and algal life, starting with plants.

1.1. The long history of development of drugs from plants

The development of medicines from plants has a long history. The very first commercial natural drug, the painkiller morphine, was extracted from *Papaver somniferum L.,* opium poppy, and marketed by Merck from 1826. The first semi-synthetic drug based on a natural product, aspirin, was isolated from *Salix alba,* a willow tree, and marketed by Bayer from 1899. Next came codeine (also from poppy), digitoxin (from foxglove, *Digitalis purpurea L.*), quinine (from the bark of the cinchona tree *Cinchona pubescens Vahl.* and other species), and pilocarpine (from the leaves of the plant *Pilocarpus microphyllus*), amongst others. Today, of the 252 drugs considered as basic and essential by the WHO, 11% are exclusively from flowering plants alone.

In recent decades, plant-derived drugs have been developed for the treatment of:

- **malaria** (Artemisinin, from the traditional Chinese medicinal plant *Artemisia annua*, Qinghao, 青蒿);
- **cancers** (e.g. Paclitaxel, originally from *Taxus brevifolia*, Pacific yew tree; Camptothecin from *Camptotheca acuminate*, the happy tree; Podophyllotoxin from *Podophyllum hexandrum and P. peltatum*, the May apple; vincristine and vinblastine from *Catharanthus roseus*, Madagascar periwinkle);
- **heart conditions** (four patented brand-name drugs containing bark-extracted quinidine from the tree *Cinchona ledgeriana*);
- **blood thinning** (the drug warfarin is derived from *Melilotus officinalis,* sweet clover);
- **chronic obstructive pulmonary disease** (a number of drugs based on tropane alkaloids (TAs) including scopolamine and hyoscyamine, derived from *Atropa belladonna,* deadly nightshade);
- **liver diseases** (from the seeds of *Silybum marianum,* milk thistle*)*;
- **pain** (from *Cannabis sativa* and *Capsicum annuum,* a variety of chilli);
- **diabetes** (from *Galega officinalis*, goat's rue);
- **Alzheimer's** (from *Galanthus nivalis,* common snowdrop);
- **Parkinson's** (from *Papaver somniferum,* opium poppy);
- **dementia** (from *Galanthus*, snowdrop, *Leucojum*, spring snowflake, Narcissus, daffodil, and Physostigma venenosum, calabar bean);
- **Tyrosinemia** (from *Callistemon citrinus,* Lemon Bottlebrush).

All of this is even though very few of the estimated 400,000 known plant species on earth[2] ever having been studied under laboratory conditions. And even this literature tends to over-estimate the true number of plants studied, because authors

[1] Newman, D. J. & Cragg, G. M. (2012); Zhu, F., et al. (2011).
[2] Govaerts R. (2001).

are often unaware of synonymy, and treat each different Latin name as if it were a different plant.

Even smaller, and indeed declining, numbers of species have been studied with sufficient rigour to be included in western health regulations. For example, the Brazilian Pharmacopoeia decreased from 196 plant species in the 1926 edition, to 32 in 1959, to 4 in 1977, before increasing again to 11 in 1996[11]. It has since risen to about 20 with the inclusion of plants involved in Chinese medicine on sale in Brazil. However, there are practically no native Brazilian plants included. In addition, although the 2010 edition cites 65 species, most are European or Asian plants, with only 14 being native to Brazil[10]. A similar trend is observed in the British Pharmacopoeia[12]. The increasing popularity in the west of Traditional Chinese Medicine (TCM) and Ayurvedic medicine (a form of traditional medicine in India) has led to some of the plants used in these medicines being included in pharmacopoeias[12], although globally the number of these species covered by formal monographs remains low. In China, for example, 10,000–11,250 species (about 34% of the native flora) have documented medicinal uses[13,14], but only 563 are cited in the Chinese Pharmacopoeia[10].

Clearly, there is a great deal of untapped potential to generate new medicines in the world of plants.

1.2. Why are plants a good place to look for new medicines?

Plants, unlike humans and animals, do not have immune systems to defend themselves against attack. Instead, they must rely on manufacturing a cocktail of chemicals that act against predation by microorganisms, insects, and herbivores. Sometimes these compounds are also active against human pathogens. For example, some parasites use similar biochemical pathways to attack both plants and humans; the compounds that plants use to defend themselves against these parasites may help humans defend themselves against parasitic diseases.

Plants have an almost limitless ability to synthesize structurally diverse compounds known as secondary metabolites. To date more than 12,000 have been isolated – which is still less than 10% of the estimated total.[3] Such compounds are not necessary for a plant's growth and function, but instead enhance a plant's likelihood of survival. Plant extracts are chemically extremely complex. A single plant extract preparation may contain hundreds of different chemical entities. In drug design this may increase efficacy against drug-resistance and, compared to synthetic products, it may improve absorption, patient tolerance, and acceptance.

The study of the extraordinary diversity of molecules manufactured by plants, and the chemical pathways plants employ, gives insights and models for manufacturing chemicals in the laboratory and in industry, and for subsequent development of new medicines. The unrealized hopes of the currently-dominant drug-development strategies have stirred renewed interest in natural products as leads for drug discovery. Since fewer and fewer therapies are being developed, and the costs of development and the prices of drug have been rising, new ways also need to be found to achieve affordability.

[3] Insert reference.

2. Plant biodiversity and medicines to tackle big health challenges

Despite all the new techniques – such as combinatorial chemistry and computer-based molecular modelling – it is proving extremely challenging to develop novel new drugs to tackle some of humankind's biggest health challenges, such as antimicrobial resistance, tropical and neglected tropical diseases (NTDs), cancer, dementia, Parkinson's, diabetes, cardiovascular disease, and many others. As a complement to the current dominant drug-discovery paradigm, natural products offer an additional route to speed up the process of discovery. Here, for now, we concentrate on plants.

2.1. Antimicrobials and drug resistance

The effective life-spans of antimicrobials – which kill or slow the spread of microorganisms, including bacteria, viruses, fungi, and parasites – become ever shorter as microbial resistance spreads, and new, particularly viral, diseases increasingly prove untreatable by current drugs. There is an urgent need to have more potential drugs in antimicrobial drug-development pipelines. Yet, the complexities and costs of drug discovery and development have led many pharmaceutical firms to shift their focus away from the development of drugs for short-course therapies, such as antimicrobials, towards drugs for long-term treatment of acute and chronic conditions. The failure of large investments into target-based approaches to produce novel antimicrobials has also encouraged many companies to leave the antimicrobial field despite the growing need.

Some new initiatives aim to boost the drug-development pipeline, such as the Global Antibiotic Research & Development Partnership (GARDP),[4] Combating Antibiotic-Resistant Bacteria (CARB-X),[5] the Pew's Shared Platform for Antibiotic Research and Knowledge (SPARK),[6] and the Innovative Medicines Initiative's Translocation project.[7] Nevertheless, there remains an acute shortage of novelty in drug concepts. Only 1 in 4 of the approximately 48 potential antibiotics currently in clinical development[8] represent a novel drug class or presents a new mechanism of action, and of these novel products only a quarter are in development for *C. difficile.* Only two are potentially active against Gram-negative ESKAPE pathogens or WHO critical-threat pathogens. Since there is a failure rate of about 80% of infectious disease drugs entering phase 1 trials, it is likely that many of these potential drugs will not obtain approval. Following the exit of large pharmaceutical companies from the R&D of antimicrobials, small companies – many of which have no revenue stream – are funding 80% of products in development, struggle to remain afloat and, even if they bring products to market, regularly file for bankruptcy.[9]

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[4] https://gardp.org. See also www.dndi.org/diseases-projects/gardp

[5] https://carb-x.org

[6] https://www.pewtrusts.org/en/research-and-analysis/articles/2018/09/21/the-shared-platform-for-antibiotic-research-and-knowledge

[7] https://www.imi.europa.eu/sites/default/files/uploads/documents/projects/IMI_AMR_2017_LR.pdf

[8] From Pew antibiotic resistance project's latest data update: http://www.pewtrusts.org/en/projects/antibiotic-resistance-project

[9] Deadly Germs, Lost Cures "Crisis Looms in Antibiotics as Drug Makers Go Bankrupt" New York Times, 25 December 2019. https://www.nytimes.com/2019/12/25/health/antibiotics-new-resistance.html

Scientists from a range of fields, in order to broaden the drug development pipeline, have restarted investigating plants and their antimicrobial properties. Laboratories around the world have found thousands of phytochemicals to have inhibitory effects on all types of microorganisms in vitro; several are being tested in humans. However, progress is slow.

There are four major groups of antimicrobial compounds made by plants: phenolics and polyphenols; terpenoids and essential oils; lectins and polypeptides; and alkaloids. In most cases, bioactive plant extracts contain complex mixtures of these groups, and it is their combined, synergistic action that yields the greatest effect. Most multicellular life, and much single-cellular life, secretes several compounds with antimicrobial properties, to attack, and more often to prevent, infection. Yet, the normal pharmaceutical practice is to treat each pathogen with one product, and most drug studies are limited to determining the activities of crude extracts of plants in vitro and/or in vivo, missing out on the benefits of the synergy of several chemicals or several plants working together.

Synergistic activity increases the obstacles for microbes to evolve resistance to a multi-sided attack. More complex chemical formulations, therefore, might outlast monotherapies and gain an advantage in the war on antimicrobial resistance. The pursuit of such a goal is undoubtedly more scientifically challenging, which has put industry and investors off.

For a pertinent example of the power of synergy, we need look no further than the antimalarial compound artemisinin, from the plant *Artemisia annua*. When artemisinin was used as a monotherapy, widespread resistance to it emerged within just a few years. Yet, *Artemisia annua* had been used in therapy for millennia (with evidence back to the Jin dynasty, 283–343 CE) without resistance developing. While the emergence of resistance may have been facilitated by the widespread, indeed global, use of artemisinin, it may also have been facilitated by the practice of isolating and using only a single compound from *Artemisia annua* rather than from exploiting the synergistic action of multiple compounds within the plant, as plants themselves do. Studies support this notion.[10] It is possible that by developing novel antimicrobial formulations that are closer to traditional remedies – involving several chemicals or even several plants – it will be possible to exploit synergistic properties in the development of future novel antimicrobial formulations designed to overcome resistance acquisition.

Furthermore, by searching only for classic bacteriostatic and bactericidal action, research strategies may have been missing out on other important possible pathways for drug action. Plant-based compounds act also on bacteria via inactivation of proteins, adhesins, and enzymes, among various targets. Some plant compounds block cell-to-cell signaling pathways, or quench production of virulence factors (e.g., exotoxins), or disrupt or inhibit the formation of the biofilms that confer a protective advantage to pathogens during an infection. Such alternative mechanisms of action are not typically part of initial drug-candidate screening. In particular, inhibitors of biofilms and toxins could potentially tip the balance back in favour of patients if used adjunctively to antibiotic therapy.[11]

[10] Insert source.

[11] Two examples: i) the chemistry of *Rubus ulmifolius*, Elmleaf blackberry, is rich in phenolics, the probable source of its antioxidant and antimicrobial activity, with potent anti-biofilm properties. Research is underway with the aim of developing products for both therapy (as an

It is also important to consider the host immune response. The typical approach to bacterial infections, of deploying antibiotics to try to kill the infectious agent, can have unintended consequences. If antibiotics damage the microflora living inside and on the surface of a human or animal body, this may open niches for other pathogens to proliferate, leading to secondary disease events, including autoimmune disorders. Synergistic plant-based compounds could reduce such risks. The mechanisms we describe below—in particular the blockchain ledger—include these as important pieces of extra information.

2.2. Tropical and Neglected Tropical Diseases (NTDs)

For large pharmaceutical companies, there is little financial return from developing drugs for Tropical and Neglected Tropical Diseases (NTDs).[12] Private-sector involvement, sometimes as part of Public Private Partnerships (PPPs) or Product Development Partnerships (PDPs), is largely motivated by non-commercial reasons, including corporate reputation. Many firms adopt an opportunistic approach, repurposing drugs previously developed for other diseases. While this reduces the costs of development – and may be a very good way in the short-term to overcome resistance pressure – it does not lead to new chemically-novel drugs which are needed in the longer term. This approach is also coming up against the problem of widespread resistance to a number of chemical classes.

Besides the evolution of resistance, in many cases current drugs suffer from low efficacy, severe adverse effects, unfavourable toxicity profiles, limited availability, and complicated treatment regimens (including the need to be given by injection). Tailoring the target product profiles of drug candidates to the needs of those in resource-poor settings is frequently not done because of the extra development costs; the use of drugs with far-from-ideal profiles can dramatically increase health-care delivery costs. Cost-effectiveness studies end up being premised on the notion that the choice is between an existing poor drug option and an even worse existing drug option,[13] although, in theory, much better (but currently non-existent) drug options might be possible. The immense therapeutic potential in natural products and their derivatives goes largely untapped.

The potential usefulness of plants is not limited to drugs. Many plants produce chemical defenses against anthropods and molluscs, which can be used to control the vectors of parasitic diseases. Many plants contain several compounds that contribute synergistically to this anti-parasitic activity. Larvicidal activity is the

antibiotic adjuvant), and infection prophylaxis (e.g., as medical device coatings); ii) Leaf extracts of *Castanea sativa*, the European or Sweet Chestnut, do not inhibit growth in MRSA isolates, but do block cell-to-cell communication. Consequently, MRSA cultures can grow in the presence of the extract but cannot produce tissue-damaging exotoxins. Research on the extract is underway to determine whether a virulence inhibitor can act as a stand-alone therapy or can be used as an adjunctive treatment with antibiotics to achieve faster resolution and recovery from MRSA infection.

[12] The current list is: Buruli ulcer; Chagas disease; Dengue and Chikungunya, Dracunculiasis (guinea-worm disease); Echinococcosis; Foodborne trematodiases; Human African trypanosomiasis (sleeping sickness); Leishmaniasis; Leprosy (Hansen's disease); Lymphatic filariasis; Mycetoma, chromoblastomycosis and other deep mycoses; Onchocerciasis (river blindness); Rabies; Scabies and other ectoparasites; Schistosomiasis; Soil-transmitted helminthiases; Snakebite envenoming; Taeniasis/Cysticercosis; Trachoma; and Yaws (endemic treponematoses).

[13] For example, HIV-associated cryptococcal meningitis, and vivax malaria.

most widely investigated property of mosquitocidal plants.

2.2.1. Malaria

The most lethal parasitic diseases, for which modern medicine has yet to find good treatments, are blood and tissue protozoa, namely malaria, the trypanosomiases, and the leishmaniases.

There have been great advances in the treatment and control of malaria. Nevertheless, in 2015, still there were 214 million cases of malaria in the world and 400,000 deaths. As antimalarial resistance (of drugs, insecticides, and, one day, vaccines) spreads, there are concerns that the current repertoire of interventions will eventually be exhausted, and mortality and morbidity will rise again.

Besides the current pipeline of malaria drugs, we need to explore under-utilised (and often under-researched) plant-based anti-malaria compounds. A few plants, such as artemisinin (from *Artemisia annua*) and quinine (from *Cinchona officinalis*), together with their synthetic analogues, have been a key source of drugs for the treatment of malaria, but there is evidence that many other plants contain anti-malarial agents. Indeed, 1,200 species of plants are known to be used to treat malaria.[14] Of 24 species from one Latin American tree genus, *Aspidosperma*, tested under laboratory conditions, 19 showed activity against the Plasmodium malaria parasite.[15]

2.2.2. Trypanosomiases

NEEDS SOME TEXT

2.2.3. Leishmaniasis

Leishmaniasis is the most neglected of neglected diseases. The first-line drugs for all clinical forms of leishmaniasis are pentavalent antimonials. Because of their greater toxicity, Amphotericin B and pentamidine are used only as second-line treatments. Numerous plant-derived natural products have been investigated as antileishmanial candidates, including various alkaloids, terpenoids, flavonoids, and quinonoids.

In Brazil, the main drug used for clinical leishmaniasis is Glucantime®, which has several adverse side effects and is costly to use. Brazil is home to an astonishing diversity of plants including many that are found only in Brazil, several of which have been shown to be active against leishmaniasis,[16] and yet little effort has been made to develop drugs for leishmaniasis based on Brazilian biodiversity.

2.3. Cancer

There have been great advances in the treatment and control of cancer, but it remains the second leading cause of death worldwide. Current treatments include chemotherapy, radiotherapy, and chemically-derived drugs. However, the toxicity of chemotherapeutic drugs and, sometimes, the undesired side effects during chemotherapy can further damage patient health. Many cancer specialists would like to see a new repertoire of affordable cancer therapies without these damaging side effects. There is some focus on using alternative treatments and therapies,

[14] Willcox, M. L. & Bodeker, G. (2004).
[15] de Paula, R.C., Dolabela, M.F. and de Oliveira, A.B. (2014).
[16] Among them, Kalanchoe pinnata, Plumbago scandens, Physalis angulata, Piper aduncum, Tabernaemontana (Peschiera) australis and Phyllanthus amarus.

many of them based on naturally-derived compounds because these are considered to have less toxic side effects than standard chemotherapy.

Plants are a reservoir of natural chemicals that may provide chemoprotective effect against cancer. Some of the compounds that plants produce to aid their own survival and for 'housekeeping' functions have demonstrated the ability to inhibit the growth and initiate the apoptosis of cancerous cells in humans. Fifteen of the 56 natural drugs registered for the treatment of cancer since 1980 were derived from plants. A myriad of other plant products – in particular, those that have been used in herbal medicine in developing countries – have shown very promising anti-cancer properties in vitro, but have yet to be evaluated in humans. For example, plant compounds that kill parasitic worms may be useful against tumors.

If plant-derived products were to reduce the adverse side effects of cancer treatment, they could increase the value of new synergic technologies, such as nano-particles for nano-medicines; these work by controlling the release of compounds, which would enhance the anti-cancer action of plant-derived drugs.

2.4. Dementia

Dementia affects about fifty million people worldwide, with Alzheimer's causing most cases. Five drugs have been developed for the symptomatic treatment of Alzheimer's disease, two of which are derived from plants. One study documented 152 plants with traditional uses for age-related brain diseases.[17] A survey of 139 different plant-derived compounds with potential to target dementia symptoms revealed the majority to be classed as alkaloids.[18]

2.5. Diabetes

Diabetes affects an estimated 422 million adults worldwide. One study documents 656 flowering plant species used traditionally for diabetes. When these data are superimposed onto genetic relationship data (a phylogeny), a high proportion are clustered in certain closely-related plant families.[19] Of 104 plants used for diabetes in seven Central American countries, for 16 there is experimental evidence that might explain their traditional use.[20] In drug discovery, *Galega officinalis* (goat's rue) provided a useful compound for the design of the anti-diabetic drug Metformin,[21] while another plant used traditionally for diabetes, *Stevia rebaudiana* (sweetleaf), is a source of sweetener compounds used in the food industry.[22]

2.6. Other Uses

It is possible that some plant species may be a source of drugs against metabolic syndrome (a cluster of conditions including high blood pressure, high blood sugar levels, and high cholesterol levels, the prevalence of which is about 33% in US adults[23]), heart conditions, HIV/AIDS, diabetes, and non-alcoholic fatty liver disease, NAFLD (the prevalence of which is up to 30% in developed countries and

[17] Adams, M., Gmünder, F. & Hamburger, M. (2007).
[18] Williams, P., Sorribas, A. & Howes, M.-J. R. (2011).
[19] Simmonds, M. S. J. & Howes, M.-J. R. (2006).
[20] Giovannini, P., Howes, M.-J. R. & Edwards, S. E. (2016).
[21] Simmonds, ibid. Giovannini, ibid.
[22] Sharma, S., et al. (2016).
[23] Aguilar M., et al. (2015).

10% in developing countries, making it the most common liver condition in the world[24]).

The treatment of many chronic conditions, that western single-drug treatments fail to address, is more effective with traditional treatments that have been employed for many years utilising many compounds/targets simultaneously. Even molecules known to be toxic may play a role in mixtures in which other molecules block their toxicity. Chinese and Indian governments and scientists increasingly recognize this, and the health systems in these countries are shifting towards employing western and traditional medicines alongside each other.

3. A summary of the obstacles to overcome

There are many obstacles in the way of exploiting the huge diversity of plant life – particularly that to be found in tropical regions – for the discovery and development of new medicines. They are grouped here under 7 main headings.

3.1 Current drug-development approaches and pharmaceutical incentives

The interest of the pharmaceutical sector in pursuing drugs based on natural products has waxed and waned. The complexities and costs of drug discovery and development, combined with a revenue model driven by blockbusters, has made many pharmaceutical firms wary of investing in a new paradigm given the already sunk costs of their current drug-discovery approaches.[25] Many have been discouraged by the perceived disadvantages of natural products. Traditional natural-product extracts are far less compatible with the high-throughput screening methods that, in the last years, have enabled companies to screen quickly large numbers of synthetic compounds in search of lead drug compounds. Indeed, large libraries of synthetic compounds have given hope to pharmaceutical companies, to the detriment of natural-product-based drug discovery research. While the hundreds of different chemical entities inside a single plant extract preparation may have many benefits – not the least of which being efficacy against drug-resistance – it is also a potential weakness: working with natural products, as compared to synthetic products, has been slower because of the complexities of natural-product chemistry. In contrast, synthetic products have often been perceived to entail lower production costs, easier quality control, more consistency and agreement on dosage, better efficacy and safety, faster effects, and more predictable side effects. However, much of this is changing, and synthetic biology may itself transform the development and production of drugs based on plant-derived chemicals.[26]

Many pharmaceutical firms have shifted their focus away from the development of drugs for short-course therapies, such as antimicrobials, towards drugs for long-term treatment of acute and chronic conditions. In the case of developing drugs for Tropical and Neglected Tropical Diseases (NTDs), there is little financial return for large pharmaceutical companies, and many new mechanisms have worked through Product

[24] Wang, Zh. Q., et al. (2013)

[25] One major pharmaceutical company that holds out a strong interest in natural products is Novartis (http://www.beautifulmedicine.com).

[26] For example, a potential anticancer drug derived from poppies was recently produced in genetically engineered yeast, with many associated benefits (such as not needing a growing season). See Li Y, Li S, Thodey K, et al. (2018).

Development Partnerships.

In order to attract investments (both public and private) into plant-based medicine development, several components of our approach need to be designed to de-risk plant-based R&D.

3.2 The need to incentivize a broader pipeline based on novelty, synergy, and mechanisms of action

In various areas of disease burden there remains an acute shortage in the novelty of drug concepts being pursued. We need to find a way to de-risk the pursuit of novelty, to broaden research from the very few plants that have so far been studied, and highlight untapped potential. The end goal is a broader drug development pipeline, and higher probability of success.

It is the combined, synergistic action of the many compounds made by plants that yields the greatest effect. The pursuit of such a goal is undoubtedly more scientifically challenging, which has put industry and investors off. Currently, most drug studies are limited to determining the activities of crude extracts of plants in vitro and/or in vivo, missing out on this synergy of several chemicals or several plants. Similarly, we need to incentivize work on alternative mechanisms of drug action, which are usually not part of initial drug-candidate screening. De-risking such activities will involve gathering and disseminating important pieces of information on novelty, synergy, and pathways of action (we visualize this below inside a block-chain ledger) and incorporating them into a rational priority setting mechanism.

3.3 IP, ownership, and the rights of indigenous populations

The current drug-discovery paradigm has been favoured by the prevalent Intellectual Property (IP) system, because of the clearer (private) property rights attached to synthetic chemicals, as compared to natural products. Pharmaceutical firms worry that their investments in natural-product research may not get fully repaid and will pit them against indigenous populations. In turn, indigenous populations worry that their plant biodiversity will be overexploited and depleted with little, or no, value coming to them; indeed, so often in the past have indigenous groups been taken advantage of that they are understandably cautious of even well-meaning efforts to establish indigenous property rights. Their governments sometimes enact legislation to protect national biodiversity that is so defensive and restrictive that it prevents good science.

Yet, without access to the abundance of indigenous knowledge in some of the poorest regions of the world, none of our goals will bear fruit. Our tools therefore have to level the playing field, enhancing access to, and scientific evaluation of the value of, biodiversity and indigenous knowledge, while supporting local ownership and fair shares of value generated by biodiversity knowledge. Meanwhile, any new tools must bolster, not undermine, the implementation of already existing protocols to protect indigenous interests.

3.4. Reliable access to biomedical and chemical research data and health records

One overlooked obstacle for those designing R&D or looking for plants (or close relatives of such plants) known to show a given activity is the widespread misuse, ambiguity, and inconsistency with which plant names are employed in the literature and health

regulation. Plants known to have medicinal activity have on average 12 scientific synonyms.[27] A search of PubMed using a single scientific name will retrieve on average only 15% of the publications indexed that relate to that plant: The missing publications will be using other synonyms. Natural product scientists have further failed to employ scientific names appropriately, publishing their work using names which apply ambiguously to more than one species or that cannot be reliably assigned to any one species. Surveys have reported 40% of scientific names used in phyto-chemistry journals (and 80% of those used in nutrition journals) to be erroneous or ambiguous.[28]

None of this could be done meaningfully using data direct from the literature or health databases as they currently stand since: it is not possible to judge the quality of research published without assessing the plant names used; many publications are ambiguous and introduce risk of misinterpretation; and the same plant is referred to by different scientific names in different journals, decades, disciplines, and countries.

3.5 Diverse dispersed data, and priority setting

Knowledge of the medicinal use and chemical study of plants is dispersed across multiple sources and disciplines, and with about 400,000 plant species, a mechanism needs to be found to exploit this huge diversity of information and focus it. Kew is building a new phylogenetic tree of plant and fungal life based on modern DNA sequencing which will enhance the ability to predict which plants share chemical pathways. To match that, we need a data-management infrastructure that incorporates data from many other sources to generate a constantly-updating priority-setting mechanism to determine the most promising potential leads and so drive research and funding priorities, to avoid replication of efforts/investments, and to further de-risk R&D activities. Machine learning offers promising computational and analytical solutions for the integrative analysis of such large, heterogeneous, and unstructured datasets.

3.6 Supporting clinical trials

To encourage more plant-based drug trials, we need to lower the risks and costs of Randomized Controlled Trials. The global partnership will need to provide a service especially for researchers working in trial networks in LMICs, to de-risk trial decisions in such settings. Those working in such networks need to prioritize targets for clinical development, including of some promising plant-based products, and invest in strengthening the relevant trial capacities. Absent good evidence on the value of plant-based research strategies, such researchers will go where the current funding flows, and sponsor priorities, are tending, and avoid plant-based drug trials. By enhancing the scientific credibility of plant-based medicines, this will also provide incentives for equipping laboratories in regions rich in potential plant-based medicines.

3.7 Protecting and valuing biodiversity and creating sustainable supply

Biodiversity could be the key to finding the next generations of medicines. And putting a value on the medical and health value of biodiversity will give stronger incentives to conserve biodiversity and innovate on the basis of biodiversity. However, if this is not to backfire, any effort to draw attention to medicines that can be derived from biodiversity will need to include measures to protect that biodiversity from short-sighted overexploitation. This will need a strategy to achieve sustainable supply, commercialization, and markets for all underutilized plants, from the start, operating

[27] Source
[28] Source

hand in hand with the development of new drugs. This will involve also taking advantage of rapid recent advances in Geographical Information System (GIS) modelling and spatial mapping of possibly suitable habitats.

In sum

A new approach is needed to break down and overcome some of the roadblocks to exploiting the huge diversity of plant life, particularly that to be found in tropical regions, in the discovery and development of new medicines. This will require the smart integration of a range of new tools, and the engagement of many stakeholders.

4. A new integrated toolbox for the research and development of plant-based medicines:

4.1. The value-added proposition

The current level of effort to research and develop new drugs from plants is out of step with the level of potential. Yet, as we have seen, there are many challenges to realizing this potential. We propose a new initiative – led, in its first phase, by the University of Oxford, Royal Botanic Gardens, Kew, Fiocruz, Brazil, and The Global Health Network, with other partners joining as soon as they wish – to build a 'common-good' platform for promoting the discovery and development of novel, affordable, and ecologically sustainable medicines derived from plants and fungi. It will serve the entire drug-development community, with components that no individual entity on its own would invest in. First, we will focus on expanding the pipeline of plant compounds as possible leads for new medicines by the rational application of a diverse body of new tools and expertise drawn from a wide range of disciplines including biology, chemistry, botany, traditional knowledge, ethnobotany, genomics, clinical science, statistics, computer science, law, Intellectual Property (IP), 'big data', block chain, economics, business studies, management, contract design, geography, anthropology, public health, epidemiology, ecology, sociology, and medical ethics. Second, some of the partners will employ their trial networks to trial potential new drugs, and other partners will expand their manufacturing activities to make new drugs available. Third, attention will be paid to a range of post-development issues, such as sustainability of production and biodiversity.

Pharmaceutical firms, as part of their already ongoing trial activities, are also interested in the more rational analysis of data, such as from using Kew's 'Medicinal Plant Names Services' (MPNS), described in more detail below, and now Kew's 'Plants for Health'. In clinical trials for new drugs, many of those enrolled are already taking herbal medicines and natural products as food supplements; those conducting the trials need to be sure what those products are and what they contain, to be able to assess any instances of adverse reactions

4.2. The collaborators

The global network will eventually, we hope, comprise the following: a range of organizations in Brazil, including the Oswaldo Cruz Foundation and its new unit in Mozambique, and the Rio de Janeiro Botanical Gardens; the Institute of Hygiene and

Tropical Medicine – IHMT, of the University NOVA of Lisbon, Portugal; the Institute of Ayurvedic Medicine, Sri Lanka; the University of Oxford, including the Department of Physiology, Anatomy & Genetics, the Oxford Chinese Medicine Research Group, the Centre for Health, Law and Emerging Tech, the Big Data Institute and the Target Discovery Institute, Medical Anthropology, the Global Health Network; the Royal Botanic Gardens, Kew, England, including a new joint initiative between Kew and Columbia; and TRAFFIC (wildlife trade specialists). Discussions are ongoing with agencies in India, Sri Lanka, China, and Germany. The goal is to have further partners in China, India, and across a variety of countries in Africa and Europe.

Brazil

The Oswaldo Cruz Foundation (Fiocruz), operating under the Ministry of Health of Brazil, is the most prominent institution of science and technology in health in Latin America, and one of the world's main public health research institutions. From its base in Rio de Janeiro, Brazil, it coordinates the activities of centres in 10 states of Brazil – in the Northeast, North, Southeast, and Southern Brazil – and 16 scientific and technical units. It has an office, Fiocruz Africa, in Mozambique. The mission of Fiocruz is to research and develop affordable new medicines for the people of Brazil, and then the world, and to disseminate new scientific and technological knowledge. Fiocruz is keen to strengthen its capacity for drug discovery and development of natural products based on the rich biodiversity of Brazil and Africa.

Fiocruz is able scale up the R&D and manufacture of trial plant-based medicines in response to evolving drug-lead priorities. In particular it is keen to identify the potential for new lines of antibiotics, antifungals, leishmaniasis, and anticancer medicines, and would aim to have at least one new Active Pharmaceutical Ingredient (API) or medicine in each of these categories.

Brazil's plant biodiversity is the highest of any country in the world. The best expertise in Brazil on this biodiversity, and the distribution of Brazilian plants, lies in the hands of the Rio de Janeiro Botanical Gardens which manages Brazil's national flora and virtual herbarium projects. This highly detailed 'local' knowledge will complement Kew's global perspective and its chemistry and medicinal plant expertise.

One goal of the partnership is for the Brazil partners to develop 'Big Data' functionality of their own, and to enhance their own open science capacity for the analysis of datasets, including of features such as regional biomes, disease vectors, and trial data. The idea of a blockchain 'Bank of Codes' (see below) is supported by the Brazilian government and is being trialed in Brazil, especially in the Amazon basin, as a possible template for the rest of the world. The Brazilian partners are well positioned for this new Global Partnership and keen to team up with Oxford, further European partners, and others to achieve their ambition.

Oxford

Oxford would contribute: interdisciplinary skill sets across numerous departments and programs; the experience of experts at the Big Data Institute and at the Target Discovery Institute (TDI) (together forming the Li Ka Shing Centre for Health Information and Discovery); specialists providing their expertise in economics, business, plant sciences, botany, microbiology, and chemistry. In 2017, Oxford's Department of Physiology, Anatomy, and Genetics set up the 'Oxford Chinese

Medicine Research Group'. Oxford groups have also generated pertinent data sets such as that of the Research Initiative for Traditional Methods (RITAM), which was set up by the Global Initiative For Traditional Systems of Health (GIFTS). The RITAM database of ethnobotanical studies of herbal anti-malarials, identifies plants that are endangered, vulnerable, or near threatened, and has been used to formulate guidelines for further studies of herbal anti-malarials.

The Global Health Network

TGHN is a knowledge exchange, training, and capacity development platform with Regional Leadership Centres in Africa, Asia, and Latin America, which aims to raise standards and support equity through access to the tools, information, and resources needed for high quality research. With nearly 400,000 registered active users and 40 million visits to theglobalhealthnetwork.org, it is the ideal place to create an open, visible, and highly accessible "natural products" knowledge hub, a place for a community of practice to grow that would deploy resources and training materials addressing needs for the research and safe use of plant-derived ingredients, substances and products. This would amplify and support the activities of Plants for Health.

The Royal Botanic Gardens, Kew, UK

Kew is the world's foremost research institution for plant diversity. In addition to its global taxonomic reference sources and un-paralleled scientific reference collections, Kew has laboratories exploring the chemical basis for medicinal activity among many plant groups including those with potential for malaria, dementia, and diabetes. In addition, Kew holds a DNA databank containing the widest representation of plant diversity in the world, which for example, together with Kew's collections, serves to provide authentication services for materials marketed as Chinese Traditional Medicines. Kew is building a new phylogenetic tree of plant and fungal life based on modern DNA sequencing which will enhance the ability to predict which plants share chemical pathways.

Knowledge of the medicinal use and chemical study of plants is dispersed across multiple sources and disciplines. Finding relevant chemical studies, reports of adverse reactions or even regulatory controls already in place is complicated by the fact that most plant species are classified in a variety of ways, under different names; thus, different scientists work on the same compounds unaware of each other, needlessly duplicating the same work or investing in studies of plants which previous work has shown not to be suitable. Different countries and different disciplines use scientific names differently. The names and taxonomy of plants are constantly changing as DNA and other data shed light on their relationships; 10,000 changes to scientific plant names are published in the literature every year.[29]

Resolving the inconsistency and ambiguity of data records and published literature is central to the Big Data goal and analysis of this Global Partnership. Kew's 'Medicinal Plant Names Services' (MPNS) has collated, organized, and rationalized more than 530,000 data records containing the scientific, pharmaceutical, and common names of medicinal plants found in 143 sources, including pharmacopoeias (Chinese, Japanese, and European editions containing technical instructions for the identification of compound medicines), medicinal plant

[29] Source

dictionaries, databases used by regulators (such as the US Food and Drug Administration), medical literature, and health regulations.[30] MPNS has recorded 28,187 species as being used medicinally (though only 4,478 are cited in regulatory publications), and is integrated with Kew's plant taxonomic references and thus automatically updates as plant taxonomy (and plant names) evolve. MPNS supplies a plant name control vocabulary and web service employed by US FDA, EMA, WHO and other health regulators as part of a new ISO drug standard. The ontogenies managed in the MPNS will support data retrieval, meaningful data analysis, and semantic linkage of the various resources of the whole of this new Global Partnership.

The interests of the Global Partnership align with those of the Underutilised Plants of Tropical Africa Hub funded by the GCRF (Global Challenges Research Fund), with the task of developing sustainable markets for plant-based products that may deliver economic benefits, improve food security, and incentivise habitat protection by local communities. The Hub focuses on five countries in Africa: Cameroon, Ethiopia, Guinea, Mozambique (where also Fiocruz has a recently-established base), and Uganda. Mali will be a knowledge exchange partner. The Hub is based on close relationships with stakeholders in Africa, built over decades of collaboration. The Global Partnership for Biodiversity, Medicine and Health will be capable of providing expertise on the medicine component of the hub, as well as the associated expertise needed for developing sustainable markets for underutilized plants.

Other partners in Africa, India, China, and Europe

The countries identified as having a very high potential interest in supporting a new paradigm for the discovery of medicines from plants include: China, India, Germany,[31] Switzerland,[32] Japan, and a number of African countries,[33] and in SE Asia. Others can join as interest grows and if the results of the initial core activities prove valuable.

In December 2016, the Chinese government, recognizing the improved scientific understanding of plants and their potential value in treating chronic conditions, announced the aim to integrate Traditional Chinese Medicine into the Chinese healthcare system by 2020, opening up possibilities for investments into new drug development.

India is also at the forefront of the development of community biodiversity registers that systematically document local resources and knowledge, and of biocultural community protocols that articulate the legal rights and responsibilities that communities have over their knowledge and resources by virtue of international and national laws.

In Africa, the four-year (2010-2014) Multidisciplinary University Traditional

[30] Currently the MPNS portal displays only the names of flowering plants and ferns (vascular plants) and does not record names of mosses (bryophytes), algae, fungi, or lichen, which are far less commonly used as medicines. MPNS may include Fungi and Lichens particularly in the future and seeks to expand to include food regulation and poisonous plant records.

[31] German Federal Ministry for Economic Cooperation and Development (BMZ).

[32] E.g., Swiss Ethnobiology Network.

[33] So far, scientists have been identified in Botswana, Cameroon, Ethiopia, Ghana, Kenya, Mauritius, and Sudan.

Health Initiative (MUTHI) was established with European Union funding (under the Framework 7 Programme) to build more sustainable plant research capacity, and research networks between key institutions in Africa (Mali, South Africa, and Uganda) and partner research institutions in Europe (Norway, UK, and the Netherlands). This capacity-building programme has ended but left a legacy of improved medical anthropological and ethnopharmacological research capacities.[34] In Oxford, the Africa Oxford Initiative fosters the establishment of equitable and sustainable collaborations between African Academics and the University of Oxford.[35]

Many of the above initiatives have come and gone. Many individuals invest time and energy in initiatives only to find them time- and funder-limited, and capacity is created then lost. There is a real sense of lack of sustainability in much of this activity that the Global Partnership will see to address.

Another interesting recent UK-instigated initiative, but with global reach, is the Queen's Commonwealth Canopy (QCC),[36] which is creating a unique network of forest conservation projects, raising awareness of the value of indigenous forests, facilitating knowledge exchange, and seeking collaborative initiatives for forest conservation.

Other organizations that might be interested in supporting the activities of the Global Partnership include: the WHO,[37] the Wellcome Trust, the US National Institutes of Health (NIH),[38] the Bill and Melinda Gates Foundation, and the World Economic Forum (WEF). The WEF is engaged in the initiative to create the Earth Bio-Genome Project (EBP) and the Amazon Bank of Codes (see below), both of which will include plant genomes.

4.3. Application of 'big data' to guide priority setting and investments

Big-Data analysis will be used to identify, probabilistically (based on all available data),[39] which plants to prioritize for clinical investigation given their drug potential. This will be in the form of a constantly updated priority-list of plant species. The data-management infrastructures will incorporate data from many and varied sources, including: ethnobotanical, pharmacological, and botanical screening efforts' participatory plant-diversity and plant-uses surveys (especially in biodiverse natural habitats); genomic analysis (see below); in vivo studies of effectiveness and toxicity, and preliminary clinical observation studies; full characterizations of all mechanisms of action, including synergistic activity and host immune response; native distribution, altitude, and habitat (provided by Kew and Rio de Janeiro Botanical Gardens); parts of plants used, the form a drug is supplied in, and other plants which are also used to make that drug (supplied by Plants for Health). The MPNS of Plants for Health will provide the means to traverse, search,

[34] See final report at https://cordis.europa.eu/result/rcn/174322_en.html.
[35] See http://www.afox.ox.ac.uk/about.
[36] See https://queenscommonwealthcanopy.org
[37] See for example, http://www.who.int/globalchange/ecosystems/biodiversity/en, World Health Organization and Secretariat of the Convention on Biological Diversity (2015). Kew is collaborating with the WHO's Uppsala Monitoring Centre.
[38] E.g., the National Center for Complementary and Alternative Medicine (NCCAM), NIH, and the Office of Dietary Supplements (ODS), NIH.
[39] The exact AI learning/sorting algorithm yet to be determined.

correct, and analyze meaningfully the various other data sets. Given the importance of natural-product sustainability, there will be an ex-ante component dealing with cost, future supply, and sustainable-commercialization (see below).

One of the data components will be plant genome sequences. The Earth Bio-Genome Project (EBP) launched in late 2015 is set to sequence, within a decade, all 1.5 million known species of eukaryotes (i.e., organisms with proper nuclei in their cells). This is a mammoth task, given how few sequences we currently have. Because of the high costs, it is being carried out in stages. At first, only one member of each family is being sequenced in detail; then one species from each of the approximately 150,000 eukaryotic genera is being sequenced in less detail. Of particular note for the Partnership is that an early data set of sequences for the Amazon Basin, the 'Amazon Bank of Codes', will be a precursor to an 'Earth Bank of Codes',[40] and offer opportunities to explore in a novel way how to adapt such data banks for the task of drug discovery, first for Brazil, and then for the rest of the world.

Literature suggests that the key to plant activity lies within clades mostly well below the family level.[41] Therefore, Kew is in the process of a major reanalysis looking at Genus level and the phylogenetic tree above that, in the hope that this will point to areas of the phylogenetic tree which will be a useful guide as to where to look for certain kinds of activity. Kew's new online portal Plant and Fungal Trees of Life (PAFTOL) is being built based on full sequencing rather than DNA BarCodes.

The difficult part will be collecting all the necessary samples for sequencing. The hope is that innovation in collection and processing (anything from use of drones to the engagement of citizen scientists/samplers) will drive the costs down. Oxford Nanopore Technologies,[42] for example, has developed a hand-held portable sequencer that might greatly reduce the costs of sequencing plants in Brazil, Africa, and elsewhere.

To further complicate matters, the concentration of active ingredients in given plant species varies greatly, depending on a range of factors, and there is no consensus as to which plants, preparations, and dosages are most effective; it may be necessary to use different plants in several different geographic areas prepared in different ways. Therefore, it may be necessary to handle data in terms of a particular remedy and not in terms of a particular plant species. Clearly, genomic data alone will not generate new plant-based drugs. More likely, such data will be more powerful if employed alongside other data sets, such as that of Plants for Health and from ethnobotany.

[40] https://www.earthbankofcodes.org
[41] SOURCE?
[42] https://nanoporetech.com.

Figure 3: The ethnobotanical approach to drug discovery can yield rich datasets of use to scientists in the chemical and biological evaluation of botanical ingredients for new molecular entities

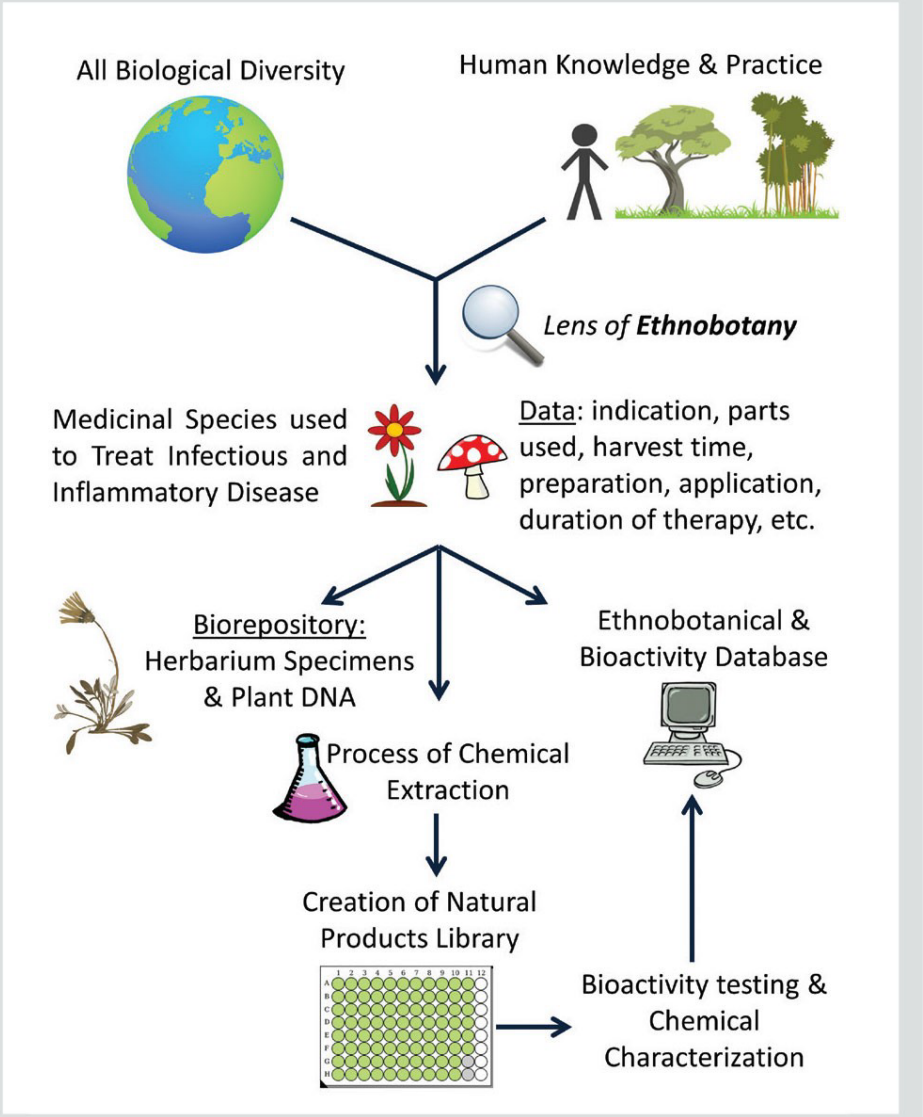

Figure 1: The stages of ethnobotany[43]

4.4. The role of ethnobotany

A key component of the MPNS, and of Plants for Health, comes from ethnobotany. Sometimes termed 'the science of survival',[44] ethnobotany focuses on indigenous knowledge systems, and covers the past, present, and future uses of plants by people. Over the ages, indigenous communities, by trial and error, have uncovered some of the ways in which plant-based compounds work against human infection and disease, and this information is embedded within the experiences and traditions of these communities.

Ethnobotany is the route to extract such data (Figure 1). It is not practically possible

[43] See http://resistancecontrol.info/rd-innovation/antibiotics-from-nature-traditional-medicine- as-a-source-of-new-solutions-for-combating-antimicrobial-resistance/

[44] See Prance G. (2007).

to evaluate all of the more than 400,000 plant species existing on Earth. Ethnobotany can be used as a lens to pinpoint those species upon which discovery efforts should be focused. Studies have shown, for example, that taking a targeted approach based on traditional medicinal uses, versus random collections of species, yields a higher success rate in identifying sources of antibacterial compounds.[45]

Ethnobotanical data may include the identities of key ingredient(s) to a remedy, indications for its use, restrictions in its use (age, gender, etc.), appropriate harvesting time, plant part(s) to be used, means of preparation (tea, macerate, tincture, etc.), mode of application (oral, topical, mucosal, etc.), storage instructions, duration of treatment, and so on.

4.5. Strengthening the indigenous country ownership stake

The potential market value of drugs derived from plants runs into many tens of billions of dollars a year. However, because of a lack of legislation and of enforcement, the royalties to indigenous populations have until now been trivial. Many large pharmaceutical, cosmetic, and food companies are based in richer developed countries, and the profit and sales taxes from exploiting indigenous knowledge go there. Indeed, despite the huge revenue potential, the value of bioprospecting contracts is estimated to be less than US$100 million a year, and most bioprospecting research contracts are very small, usually under US$1 million each.[46]

Both drug developers and indigenous populations worry about the IP (Intellectual Property) of, and access to, plant materials. A key goal of the Global Partnership will be to enhance the value of natural resources to populations of countries and indigenous regions where the natural resources are to be found, whilst also protecting those natural resources from overuse, and achieving sustainability of biodiversity. A corollary will be to attract fresh public- and private-sector investors, including into small companies (which will value the public good that the Partnership will provide but would never individually be able to provide it).

To improve the entitlements of the owners of natural product knowledge, the United Nations Convention on Biological Diversity and its supplementary agreement, the Nagoya Protocol,[47] seek to give rights to the countries of origin of natural biological knowledge. The protocol requires negotiation of equitable access and benefit-sharing agreements before any research can take place. However, the protocol does not cover all potential users of natural knowledge and there is risk of biopiracy and IP theft by non-signature countries. In the case of plants, there is also confusion over which plants to protect because of the lack of precise naming, and evidence of misuse of information as plants are confused and substituted because of the lack of precise identity. Protecting IP based on a single scientific name for a plant is not effective. Patent offices, unaware of this, could in principle be establishing umpteen patents for the same plants.

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[45] See Quave CL, Plano LR, Pantuso T and Bennett BC. (2008); Khafagi IK. and Dewedar A. (2000).
[46] An example is the agreement signed between the Union of Zapoteco Chinanteca Communities in Mexico and the Swiss firm Novartis. Novartis agreed to pay between US$1 and US$2 million for each active compound. GlaxoSmith Kline and the biotechnology company Extracta in Brazil made a transacted agreement worth US$3.2 million for the collection of 30,000 samples.
[47] See https://www.cbd.int/abs/about/

Even with the protocol, protection of traditional knowledge has often been weak. Adherence to the agreed terms requires capacity to enforce laws, trade agreements, and international treaties. Because countries and indigenous communities have unequal capacities to negotiate contracts with multinational companies, benefit sharing has not been equitable. For example, after ACE inhibitors (used to treat high blood pressure and heart failure) were derived from snake venom, no royalties or tax revenues were paid to those in the Amazon basin where the knowledge first originated; most profits were appropriated by foreign companies. Yet also, regulations to protect the rights of the protocol can also dissuade some companies from researching into plant-based medicines.

The FairWild Standard[48] and certification system[49] also provide a framework for verifying that the collection of wild-harvested medicinal plants is sustainable, and that trade is equitable. During the development of the FairWild Standard, several pilot projects were carried out in India, and are underway in Asia, South America, Africa, and Europe.[50] In China, as part of the EU-China Environmental Governance Programme, a project is experimenting with promoting sustainable sourcing, in line with the FairWild Standard, in the traditional Chinese medicine sector. This range of existing partnerships could be part of a financial support mechanism to promote research and development, as well as capacity development, for plant-based medicines. FairWild is already partnering with Kew's MPNS, and the Global Partnership would identify how MPNS might better support FairWild's import and supply-chain work.

The Global Partnership will also take advantage of rapid recent advances in Geographical Information System (GIS) modelling and spatial mapping of possibly suitable habitats (similar to the system defining 'terroir' regions for wine appellation and regulation around the world). Kew has extensive experience using GIS mapping and modeling to advise the Ethiopian Government where to invest to grow coffee in the future given climate change. The mapping inputs – as well as climate, elevation, precipitation, etc. – might also include ethnobotanical evidence, fieldwork-based research, and parallel studies on the biodiversity of a region. Fiocruz is keen to have a better map of the biodiversity (genes, species, and ecosystems) and potential of each region in Brazil and the Brazilian Amazon, to better grasp what Fiocruz calls the 'Local Ecoproductive Arrangements' (Arranjos Ecoprodutivos Locais, AEPLs).

While partners in Brazil, India, China, and elsewhere are well-placed to develop novel technologies for the cultivation and production of plant-based medicines, industry needs to invest in cultivation too. Such investment is more likely if cultivation is given higher value, as will be the case if there is greater certainty that

[48] See http://www.fairwild.org.
[49] See http://www.fairwild.org/certification-overview.
[50] An example is the ISSC-MAP (International Standard for Sustainable Wild Collection of Medicinal and Aromatic Plants) in India, under the project 'Saving Plants that Save Lives and Livelihoods', supported by the German Federal Ministry for Economic Cooperation and Development (BMZ), and implemented by FRLHT and TRAFFIC India. In Karnataka, India, scientists and community members, mapped resources and elaborated a sustainable harvesting strategy. A FairWild Standard certification pilot study is underway in the Western Ghats, with the financial support from the UK's Department for International Development (DfID)/Department for Environment, Food and Rural Affairs (DEFRA) Darwin Initiative and the Keidanren Nature Conservation Foundation. The FairWild Standard has also been implemented in other countries of Asia, South America, Africa and Europe (Kathe et al. 2010).

production will be bought (for example, by virtue of the blockchain described below).

4.6. Blockchain, genome, and sequence data

A more robust implementation mechanism is needed if the Nagoya Protocol and FairWild Standard are to achieve their full potential and pull large investments into the development of novel new drugs based on natural products – in our case, plants. It has recently been proposed[51] that a blockchain could be used to reassure both indigenous populations and investors that their interests will be protected, and to stimulate sustainable use of natural resources. The idea is to create an open library of genomic data, contained in a blockchain ledger. The blockchain would track who does what with what data. Those using the knowledge in the blockchain would be required to enter into a contract (possibly an automatic 'smart contract' that would monitor and execute itself) which would track their use of the data (if they wished to benefit from payments later, they would be obliged to enter truthfully into the blockchain leger any use they make of data already contained in the blockchain leger as well as any new data they generate), such that the blockchain-ledger would update in real time. If the knowledge became commercialized – for example if a new drug was licensed – profits would be shared across all the owners of the knowledge. In principle, this would help prevent biopiracy – since everyone's actions would be traceable and transparent – whilst also encouraging use of the data. A big potential advantage of a blockchain is that the data, and the science, would be open source even if profits might be earned and shared. A pilot version of how this would work for the Amazon Basin – an 'Amazon Bank of Codes' – is currently being worked on with the support of the World Economic Forum. This is the prototype for an eventually worldwide 'Earth Bank of Codes', which might also be contained in a blockchain. Fiocruz is in the advantageous position of having scientific bases all over Brazil and good support of the Brazilian government, and the 'Amazon Bank of Codes' has piqued the interest of the Brazilian and Peruvian governments.

There is no reason why the blockchain could not be thought of as an even larger data infrastructure, containing multiple datasets, potentially far beyond genome sequence data, with rules for usage and updating to be followed by all 'contracted' parties. The vision of the Global Partnership is to allow the plant-based MPNS database of Plants for Health to interact with many other databases inside a blockchain, becoming part of a plant-knowledge blockchain ledger. The blockchain would be not just a public-good store of data, but also the heart of a collective priority-setting mechanism – to which all parties would have formally agreed in advance – that would guide research and development and investments. The blockchain ledger would involve a continuously updated list of scientific plant names, plant parts cited in each of any remedies, harvesting information (indicating who is harvesting, where, when, how much, and whether it is sustainable), regulations concerning plant collection permits and export/import permits, preparations, dosages, evidence of synergistic action, trials performed/to be performed, efficacy results, etc. Users would be required, and incentivised, to record such information to be able to benefit from any future payout.

[51] A key proponent is Juan Carlos Castilla Rubio. Some herbal medicine professional associations are also looking to use a similar approach and some early steps are being taken.

Fiocruz proposes that one component of the blockchain will be the more than 100 million patents available in the EPO (European Patent Office) database (identified, extracted, and processed via big data algorithms, according to the health priorities of the Partnership, the possibilities for innovation through biodiversity, the benefit to global health, and relevance to the bioeconomy of Brazil).

Planning for access to plant specimens can sometimes be difficult, especially in an international setting. The blockchain would be used to put countries in charge of local specimens and of the IP coming from them, with access controlled by access agreements stored in the blockchain.

The information in the blockchain could also be used to tackle counterfeits, to monitor and control overharvesting, and to help achieve sustainable production (see below). Counterfeits are a major driver of resistance to some medicines; those not recording their activity in the blockchain would be deemed to be manufacturing and/or selling counterfeits. The community biodiversity registers and biocultural protocols – described above – provide pointers to the terms of engagement of communities in India, China, and elsewhere, and might also find a place in an expanded blockchain.

Laboratories of the world have found literally thousands of phytochemicals which have inhibitory effects on all types of microorganisms in vitro. It would be useful to standardize methods of extraction and of in vitro testing so that the search could be more systematic, and the interpretation of results could be facilitated. The real-time current best-practice on this could also be recorded within the blockchain.

Many key issues still need to be resolved, and the considerable challenges in making the above blockchain operational must not be underestimated. For example, if open-source information is stored in the blockchain, what if a public entity seeks a not-for-profit price, but a private firm seeks a much higher price? Does pricing policy have to be part of the blockchain rules, in contrast to the current practice of letting firms negotiate price after licensing? What if, for example in the case of antimicrobials, the payment mechanism includes a supply constraint (so that new antimicrobials are not overused), such that developers who use the underlying intellectual property agree to be bound by this supply constraint even before engaging in any development? (could antimicrobials even be used as a pilot for such an arrangement as part of a subscription-based model of payment for new antimicrobials?). Decisions on such rules are likely to involve complex economic logic. How would adherence to the rules be monitored and enforced ex post? Could deviators be punished? What if firms currently working on particular natural products wished to opt out for these, or related, products? If the blockchain creates value because it is a coordination device, one can visualize, at least in theory, using rules to incentivize firms to put certain data into the public blockchain rather than keeping it private, but the practical reality might be very different. How would the rules deal with 'good' and 'bad' private-sector withholding of data? Studying the problem through the lens of game theory and the economics of bargaining might prove fruitful.

An effective blockchain will require more work on legal agreements, royalty contracts, contract negotiations, and enforcement. The blockchain ought to contain rules that would be updateable and at all stages transparent and self- enforcing. However, working out contract terms ahead of something so potentially

complicated will be challenging. Terms fair to all sides will need to be determined beforehand, to avoid the hold-up problem (whereby those investing in local knowledge risk the other side reneging on contract terms and, aware in advance of this risk, they do not invest in local knowledge in the first place). There might need to be a tradeoff between making the rules adaptable (so that they can be more efficient in response to changing information, even if this increases uncertainty and the possibility that the rules will be gamed) and having fixed rules (to create more certainty and less manipulation, even if this increases the inefficiency of the rules in response to changing information). It will also, probably, require better ex ante valuation of biodiversity and, specifically, of plant-based biodiversity, which is an issue to which we shortly turn.

4.7. Protecting biodiversity and ensuring sustainable supply

Any effort to draw attention to medicines that can be derived from biodiversity will need to incorporate measures to protect that biodiversity from short-sighted overexploitation and to manage longer-term sustainably. Biodiversity could be the key to finding the next generations of medicines. Yet, humankind is destroying global biodiversity at an alarming rate. Another driving factor for the renewed interest in plant antimicrobials in the past 20 years has been the rapid rate of (plant) species extinction.

The drug discovery process itself requires only tiny amounts of materials. However, when drug manufacturing is being scaled up, the risk of depleting biodiversity rises. Overharvesting may lead to early depletion not only of plants that are already generating medicines, but also of plants that might have led to future medicines.

For example, the chemical in the four cardiac drugs mentioned in section 1.1 above cannot be copied in a laboratory (unlike the plant chemical quinine from the same tree): the bark of the rainforest tree *Cinchona ledgeriana* must be harvested to make the drug. Similarly, the bark of the *Prunus Africana*, a cherry tree that grows in mountainous regions in Africa and is used as a treatment for prostate enlargement, is also harvested; in the past, the bark was only partially harvested so that trees would recover and live to be re-harvested, but tree population are now gradually being wiped out, as trees are being totally stripped or felled for their bark.

There are plenty of other plant species, and associated medicines, already under threat, including:

- tetu lakha (*Nothapodytes foetida*), a small tree found in rainforests in south India and Sri Lanka and used for anticancer drugs;
- a saw-wort known as costus or kusta (*Saussurea lappa*) from India, the root of which is used for chronic skin disorders;
- the tendrilled fritillary (*Fritillaria cirrhosa*) from Sichuan, China, used to treat respiratory infections.

Currently, the bigger problem is the rapidly expanding global demand for herbal remedies, drawing off an already declining population of plant species. The problem is not confined to poorer countries. The global market for herbal medicines was estimated in one recent market report to be US$110.2 billion in the year 2020, and projected to reach US$178.4 billion by 2026, a CAGR of 8.1% over that period.[52]

[52] Global Industry Analysts Inc., (GIA) "Herbal Medicines - Global Market Trajectory & Analytics",

China is forecast to reach $32.9 billion by 2026, a CAGR of 10.8% over the period. Many wealth countries are experiencing rapid rates of growth too; Japan, Canada, Germany have forecast CAGR of 7.4%, 7.1%, and 6.5% over that period. Many firms source all their plants from the wild in India and China without a thought to long-term sustainability. Of the 50,000-70,000 known medicinal and aromatic plants used industrially, only about 900 are cultivated and, even then, only a very small number of firms grow supplies, and they do so only to satisfy very small proportions of their needs. In India, about 80% of medicinal plants are collected from the wild,[53] and around 300 plants and a few faunal species are under threat.[54] China is at particular risk from the expansion in use of Traditional Chinese Medicine. The impact is felt in countries neighboring China too, since China now imports certain plant species from them. The lack of incentive to invest in sustainable supplies of particular species is also in part being driven by changing health fads, which shift demand from species to species. This is reinforced by a lack of awareness amongst consumers regarding sustainability of their supplies.

To tackle many of these problems, there will need to be a sustainable supply/commercialization strategy worked out in advance, operating hand in hand with the development of new drugs and the spatial mapping of possible habitats. It will also be necessary to monitor and predict the increase in demand for natural raw materials consequent on increased drug discovery. One proposal is for a kite mark to identify sustainably-harvested products (the evaluation of which could be part of the blockchain mechanism). The work of Kew and its partners on supply chains is pertinent. The British Herbal Medicine Association and other trade bodies are also taking action in the absence of legislation.

4.8. Valuing and protecting biodiversity

New policy forums, such as the Intergovernmental Platform on Biodiversity and Ecosystem Services (IPBES), are exploring ways of assessing the economic value of biodiversity and 'ecosystem services'. There are calls for an equivalent for biodiversity to the Stern Report on the economic impact of climate change. This would analyze the global economic value of biodiversity, as well as the costs of the loss of biodiversity and of the failure to take protective measures versus the costs of effective conservation. Medicines, and potential medicines, are one of those economic values.

Putting a figure on the medical and health value of biodiversity will have a number of valuable side-benefits, all of which will need to be carefully assessed and not simply presumed: it will promote technology and knowledge transfer among countries (North-South and South-South); it will give stronger incentives to conserve biodiversity because local populations will be more aware of the potential medical and economic value of local natural habitats and they will protect them as a resource to support local livelihoods; it will promote innovation, helping countries to develop new pharmaceutical products; and it will enhance employment opportunities linked to the use of natural products. With a shift to a 'bioeconomy', the Amazon basin would shift away from mining, logging, and ranching, towards exploiting the biological information contained in indigenous

October 2021, https://www.prnewswire.com/news-releases/a-178-4-billion-global-opportunity-for-herbal-medicines-by-2026---new-research-from-strategyr-301400269.html

[53] Foundation for Revitalisation of Local Health Traditions, FRLHT (1999), and FRLHT (2009).

[54] FRLHT 2009, ibid.

living organisms and enhancing biodiversity sustainability.[55] A similar affect can be expected in China, India, Africa, and elsewhere. Of course, in all places there will be vested interested wishing to do the opposite.

The unique plant diversity, richness of ecosystem services, and abundance of indigenous knowledge in some of the poorest regions of the world are key for achieving the UN Sustainable Development Goals (SDGs). Enhancing access to, and scientific evaluation of, such resources and knowledge – if it can be done in a way that is fair and equitable for those living in such regions – may lead also to new ways to support the SDGs.

4.9. Supporting clinical trial capacity

The benchmark of medical research and evidence-based medicine is the Randomized Controlled Trial (RCT) performed on human subjects, comparing outcomes of those receiving experimental drugs and those receiving already known drugs or placebos. However, RCTs are expensive and time-consuming. As a result, there is little clinical data on safety and efficacy of many natural products, including those that are derived from plants. Often, the evidence of efficacy is anecdotal – that patients got better even if improvement with time was probable even without the treatment.

The collection of clinical plant-based data may be encouraged during ethnopharmacological field studies, but dose-escalating prospective studies (comparing outcomes according to doses of a treatment) are rare, and randomized controlled trials are rarer still. There are three stages to the work of the Partnership. The first is the creation of the best possible evidence base for the most efficient, less wasteful, rational hunt for new drug leads based on plants. The third, and last stage, is the easing of a range of post-trial issues, such as sustainable supply, property rights, royalties, fees, etc. The second, and middle stage, of interest to some of the partners in the Partnership, relates to the conducting of trials of potentially novel new drugs, alongside more 'traditional' synthetic chemical candidates. The Partnership will provide a service for trial networks and to support research capacity strengthening – such as of the 'Global Health Network' and 'Oxford in Africa' – that are considering how to prioritise clinical development, including of some promising plant-based products.

The Partnership, by lowering the risks and costs of RCTs, will encourage more plant-based drug trials. By enhancing the scientific credibility of plant-based medicines, it will provide incentives also for equipping laboratories in regions rich in potential plant-based medicines.

4.10. The economics of biodiversity

A critical part of the problem, and therefore of the solution, lies in economics. The Partnership will include ongoing development and application of economic methodology to:

i) Evaluate beforehand the expected cost effectiveness of, for example, superior antimicrobials or drug product profiles closer to the needs of those in resource-poor settings. It is usual to calculate cost effectiveness once a product

[55] Of course, this shift will face the counteractions of vested interests.

exists, by which time the choice of product is a *fait accompli*. However, to help guide priorities, it will be imperative to have some notion of expected cost effectiveness very early in the development process. The research focus would be helped if the costs and benefits of, for example, synergistic compounds could be derived. Do the benefits justify the investment? Is the short-term more difficult 'synergistic' route the better route in the long-term?

ii) Provide investment advice.

iii) Set up natural capital/asset accounts/registers, and natural capital balance sheets, with a particular focus on medicines as biodiversity assets.

iv) Explore affordability.

v) Value and identify at-risk plants.

vi) Value biodiversity and the economics of ecosystems.

vii) Develop locally-specific commercialization pathways that prioritize the value of plant diversity for local communities.

Conclusion

We have only scratched the surface in our understanding of the chemical diversity and bioactivity of plant natural products. Indeed, with only about 20% of the world's 110 million plant and animal species officially classified,[56] most of the potential remains unseen. This new Global Partnership will draw off a range of strengths that already exist. It will add some critical new features to make the whole greater than the sum of the parts. It will help to invigorate the search for plant-based solutions to some of the 21st century's biggest health challenges, whilst, into the bargain, providing additional ways to support the Sustainable Development Goals.

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