Global Partnership for Biodiversity, Medicine and Health

Introduction:

Despite scientific and technological advances, it is proving difficult to develop new medicines to tackle some of humankind's biggest health challenges: antimicrobial resistance; neglected tropical diseases; cancer; dementia; diabetes; and cardiovascular disease. We propose a new initiative to build a "common-good" platform for promoting the discovery and development of novel, affordable, and ecologically sustainable medicines derived from plants, fungi, and algae, starting with plants. We will focus on the extraordinary diversity of plant, fungal, and algal life and pilot tools that are transferable across, and potentially scalable to, all natural product R&D. After four years of discussions, it is proposed that the University of Oxford, Royal Botanic Gardens Kew, the Oswaldo Cruz Foundation (Fiocruz) of Brazil, and The Global Health Network coordinate a first round of workshops. Others (see below) will join as and when it suits them.

Natural products were the initial source of half of the medicines approved between 1981 and 2010 (593 of 1130).[1] Plant-derived medicines have already been developed for the treatment of malaria (the main ingredient of current combination therapies is derived from a plant), cancers (15 of the 56 natural drugs registered for the treatment of cancer since 1980 are derived from plants), dementia (2 of the 5 drugs developed for the symptomatic treatment of Alzheimer's disease are derived from plants), heart conditions, chronic obstructive pulmonary disease, liver diseases, pain, and diabetes. Of 252 drugs deemed essential by the WHO, 11% are exclusively from flowering plants.

Yet less than 5% of the estimated 400,000 known plant species on earth have been studied in the laboratory for their bioactivity and medical properties. This suggests that if current barriers can be overcome, there is huge untapped potential for novel medicines derived from plant biodiversity.

The antimicrobial power of plants

To fight off predation by microorganisms, insects, and herbivores, plants have evolved to manufacture cocktails of chemicals that may also be active against human pathogens. About 12,000 structurally diverse compounds have been isolated, but these are estimated to be less than 10% of the possible total.[2] In most cases, bioactive plant extracts contain complex mixtures of compounds, the combined, synergistic, activity of which – and their ability to mount a multi-sided attack – making it hard for microbes to evolve resistance. Plants could therefore be an ally in our fight against antimicrobial resistance. There have been great recent efforts to boost the numbers of antimicrobials in development, but the pipeline is crucially lacking in novelty of drug class and mechanism of action, which plants have the potential to fill.

Plant-based compounds also act on bacteria by inactivating proteins, adhesions, 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 complexity advantages plants but acts as a significant barrier to the engagement of pharmaceutical firm.[3] Such firms prefer the more straightforward IP rights

[1] Newman, D. J. & Cragg, G. M. (2012); Zhu, F., et al. (2011).
[2] Source?
[3] One major pharmaceutical company that holds out a strong interest in natural products is Novartis

attached to synthetic chemicals than working with plants which may have been used traditionally for similar purposes.

About 50 people have been involved in shaping the vision for a Global Partnership for Biodiversity, Medicine and Health. Our conceptual framework is visualized in the attached figure. We have three initial focus areas.

Focus Area 1: Joint data and science package and blockchain: search and priority-setting mechanism

The first is a collection of components that create a global public good based on open science principles.

The 'Oxford Plants to Population: Drug Discovery Centre Oxford-China', set up in 2017 in the Department of Physiology, Anatomy, and Genetics, is applying a range of scientific tests – see 'Science Package' in the figure – to just two Chinese medicines as pilot cases. New data sources and recent developments in machine learning give a unique opportunity to extend this pilot by bringing together dispersed, large, heterogeneous, unstructured data sets, across multiple sources and disciplines, to search across all known plant biodiversity on earth for candidates for further investigation in the science package/discovery centre(s).

Plant names, phylogenetic tree of life, ethnobotany, and other studies:

A key barrier has been the widespread misuse, ambiguity, and inconsistency of plant names in the literature and health regulations.[4] The taxonomy and thus names of plants are also constantly changing as DNA and other new data shed light on their relationships: 10,000 changes to scientific plant names are published every year. The 'Medicinal Plant Names Services' (MPNS) of Royal Botanic Gardens, Kew, England, has collated, organized, and rationalized more than 530,000 data records containing the scientific, pharmaceutical, and common names of medicinal plants found in 153 sources (covering hundreds of individual monographs), including all major pharmacopoeias, medicinal plant dictionaries, databases used by regulators (such as the US Food and Drug Administration and World Health Organization), and medical literature. The MPNS is automatically updated as plant taxonomy evolves, and will be the means to traverse, search, disambiguate, retrieve, correct, integrate, and analyze the various other data sets from medical and chemical studies.[5] 'Plants for Health' builds off and expands the MPNS.

Royal Botanic Gardens, Kew, also hold a DNA databank containing the widest representation of plant diversity in the world, and is building a new phylogenetic tree of plant and fungal life based on DNA full sequencing. With other components of the joint data package and machine learning, it will be possible to search for areas of the phylogenetic tree where similar pathways of chemical action and medicinal effects are concentrated. Kew has recently approved funding to expand its MPNS to all plants relevant to public health, 'Plants for Health', and would like to start linking this body of work to the proposed 'Global Partnership for Biodiversity, Medicine and Health'.

The other key data include: ethnobotanical (which focuses on indigenous knowledge

(http://www.beautifulmedicine.com).

[4] Plants known to have medicinal activity have on average 12 scientific synonyms. 40% of scientific names used in phyto-chemistry journals and 80% of those used in nutrition journals are erroneous or ambiguous.

[5] A search of PubMed for published data concerning a plant using one of its scientific names will on average retrieve only 15% of the literature actually indexed by PubMed concerning that plant: the remainder of publications having employed alternative synonyms.

systems, and covers the past, present, and future uses of plants by local populations);[6] participatory plant-diversity and plant-uses surveys and the results of in-depth fieldwork (especially in biodiverse natural habitats); pharmacological and botanical screening efforts; in vivo studies of effectiveness and toxicity; preliminary clinical observation studies; native distribution and habitat; etc.

The science package/discovery centre(s):
The science package – plant science, pharmacology, physiology, population science – incorporates the activities of the 'Oxford Plants to Population: Drug Discovery Centre Oxford-China' (see figure), to understand underlying physiological processes and potential population impacts of plant-based medicines. Royal Botanic Gardens, Kew, also has laboratories exploring the chemical basis for medicinal activity among many plant groups with particular potential for malaria, vascular dementia, and diabetes.

The blockchain:
We will explore how to fit together the data and science packages by means of an open-science blockchain at the heart of a collective priority-setting mechanism. The blockchain ledger will hold an open library of plant names and all the above data, with rules for usage and for updating to be followed by all research parties. The MPNS database would curate the data inside the blockchain, becoming part of a plant-knowledge blockchain ledger. Machine learning will generate a constantly updating real-time two-part priority algorithm for selecting which plant species to submit to the science package for further investigation, with the results fed back from the science package into the data package. The second part of the priority-setting algorithm will narrow down from those plant species that went through the science package to those that will proceed to further preclinical studies and clinical trials.

Focus Area 2: Valuation and protection of biodiversity – the case of medicine and health

This initiative grew – over several years and across meetings in Brazil – out of the interests of researchers in Oxford and Fiocruz, Brazil to find a win-win way to protect Brazilian biodiversity while strengthening the capacity of Fiocruz to discover and develop medicines based on the rich biodiversity of Brazil and Africa (Fiocruz has a new unit in Mozambique). This has evolved towards an initial collaboration between the University of Oxford, Royal Botanic Gardens, Kew, the Oswaldo Cruz Foundation (Fiocruz) of Brazil, and the Global Health Network , to which it is planned a range of other country partners will join when it suits them.

Brazil's biodiversity
Biodiversity is the most under-developed part of 'natural value'.[7] A high proportion of global biodiversity is found in tropical forests, such as those of Brazil, which are being destroyed at an alarming rate. In January 2022, according to satellite data, record high deforestation was recorded in Brazil [8] Focus Area 2 will calculate the changing expected value of plant and fungal biodiversity for medicines, potential medicines, and health, and the costs of failure to take protective measures versus the costs of effective conservation. If we aim to enhance the value of natural resources to populations of countries and indigenous regions where the

[6] Involving a thorough ethnobotanical/medical anthropological reading of existent literature, because there is insufficient (significant and consequential) detail in current data sets/records.
[7] The literature mostly uses the economic phrase 'natural capital' but we wish to emphasise issues beyond the economic.
[8] "Amazon deforestation: Record high destruction of trees in January" https://www.bbc.co.uk/news/science-environment-60333422

natural resources are found, we need to know the current baseline from which we start. How might climate change and other human disturbances affect this value? Fiocruz is keen to have a better map of the geographical distribution of biodiversity (genes, species, and ecosystems) and the potential of each region of Brazil and the Brazilian Amazon; the partners will employ recent advances in Geographical Information Systems (GIS), and work with others with an interest in biodiversity mapping, to derive and show this.

Local people are usually the first to want to preserve local plant systems, but they are often forced to do otherwise by a political economy beyond their control. Economic arguments highlighting the value of local plants, not only for their medicinal potential but also for the many other roles they perform (including carbon sequestration, flood protection, and other ecosystem services), could be powerful tools for engaging industry and government in learning about the value of biodiversity, and for exploring how local populations may benefit from it. With a higher-value local 'bioeconomy', the Amazon basin might shift away from mining, logging, and ranching, towards utilizing the biological information contained in indigenous living organisms, enhancing biodiversity sustainability.[9] A similar affect might be expected in Africa. This will complement the work of Kew's 'Plants for Health' with the World Intellectual Property Organization to facilitate both protection of rights in traditional knowledge and reliable access to such established rights for researchers and companies: Not knowing what can be developed is a huge barrier facing the research and development of novel plant medicines.

Indigenous ownership:
This might all backfire unless we create a mechanism to protect plant biodiversity from any short-sighted overexploitation that our activities might inadvertently encourage. Since our approach involves access to the abundance of indigenous knowledge in some of the poorest regions of the world, participatory approaches with local peoples will be vital. Indigenous groups are aware of their role as custodians of much of the world's biodiversity and have a close relationship with plants and animals in their environs. Yet, they have too often seen their knowledge exploited with little, or no, value coming to them.[10] The blockchain will incorporate at every step the legal and ownership rights of indigenous knowledge holders, storing and curating Prior Informed Consent (PIC) agreements of local medicinal plant knowledge holders, and Access and Benefit Sharing agreements (complying with Nagoya/CBD) that give fair shares of value generated by biodiversity knowledge. The information in the blockchain could be used to tackle biopiracy and illegal trade, as well as help to achieve sustainable production and biodiversity management. Exploration of the potential uses of blockchain in open-science R&D systems is ongoing in Oxford, and further development is an early priority of the partners.

There are considerable challenges in making all of the above operational, notably the creation of legal agreements, royalty contracts, and enforcement rules that would be updateable, transparent, self-enforcing, and truly involving indigenous stakeholders. It is not obvious how to calculate the value of the information of indigenous knowledge holders and to share benefits once a product is commercialised (a major barrier to all natural product research and development). Tackling these issues will need the skill sets of those who work in nature conservation, sustainable biodiversity, legal studies, and earth juisprudence.

[9] We recognize the challenge of vested interests.
[10] 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 despite protocols designed to ensure this.

The potential advantage of blockchain technology is that it will openly track transactions and potentially provide a record of any value being added. If we can demonstrate that this novel application of blockchain technology works for these sorts of interactions, this would in itself be a hugely valuable finding.

Focus Area 3: Low-cost pilot study

FA1 and FA2 cover the first steps towards creating a network of collaborating biodiversity, medicine and health institutes. Before a large investment, we visualize a low-cost pilot study as proof of principle – on plants in Brazil (and possibly Africa) as a pilot for all plants, and on plants as a pilot for all natural products. Brazil is the ideal candidate, as it has the highest plant biodiversity of any country in the world. Fiocruz 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. It seeks at least one new plant-based Active Pharmaceutical Ingredient (API) or medicine in each of four areas: antibiotics, antifungals, leishmaniasis, and cancer. The partners will explore a pilot involving researchers in Africa too.[11]

Africa: Anthropological and ethnopharmacological research

Strong interest has been expressed by African researchers, whose engagement with the Global Partnership for Biodiversity, Medicine and Health we need to strengthen and, indeed, invest in. The four-year (2010-2014) EU-funded Multidisciplinary University Traditional Health Initiative (MUTHI) left a legacy of improved medical anthropological and ethnopharmacological research capacity in Africa (Mali, South Africa, and Uganda),[12] but without proper investment such capacity is being lost. In Oxford, the Africa Oxford Initiative fosters the establishment of equitable and sustainable collaborations between African Academics and the University of Oxford.[13] Scientists from Botswana, Cameroon, Ethiopia, Ghana, Kenya, Mauritius, and Sudan who have a potential interest have been identified. The partnership's activities also align with, and will contribute a medicine and health angle to, the Underutilised Plants of Tropical Africa Hub funded by the Global Challenges Research Fund (GCRF) to develop sustainable markets for plant-based products (in Cameroon, Ethiopia, Guinea, Uganda, Mali, and Mozambique). Little clinical data exists on the safety and efficacy of many natural products, including plant-derived ones. Dose-escalating prospective studies are rare, and randomized controlled trials are rarer still. Clinical trial networks – such as those of the Oxford-initiated 'Global Health Network' and 'Oxford in Africa' – and those who fund such activities will only invest in strengthening natural-product trial capacities when there is more evidence of scientific credibility, which this partnership will aim to provide.

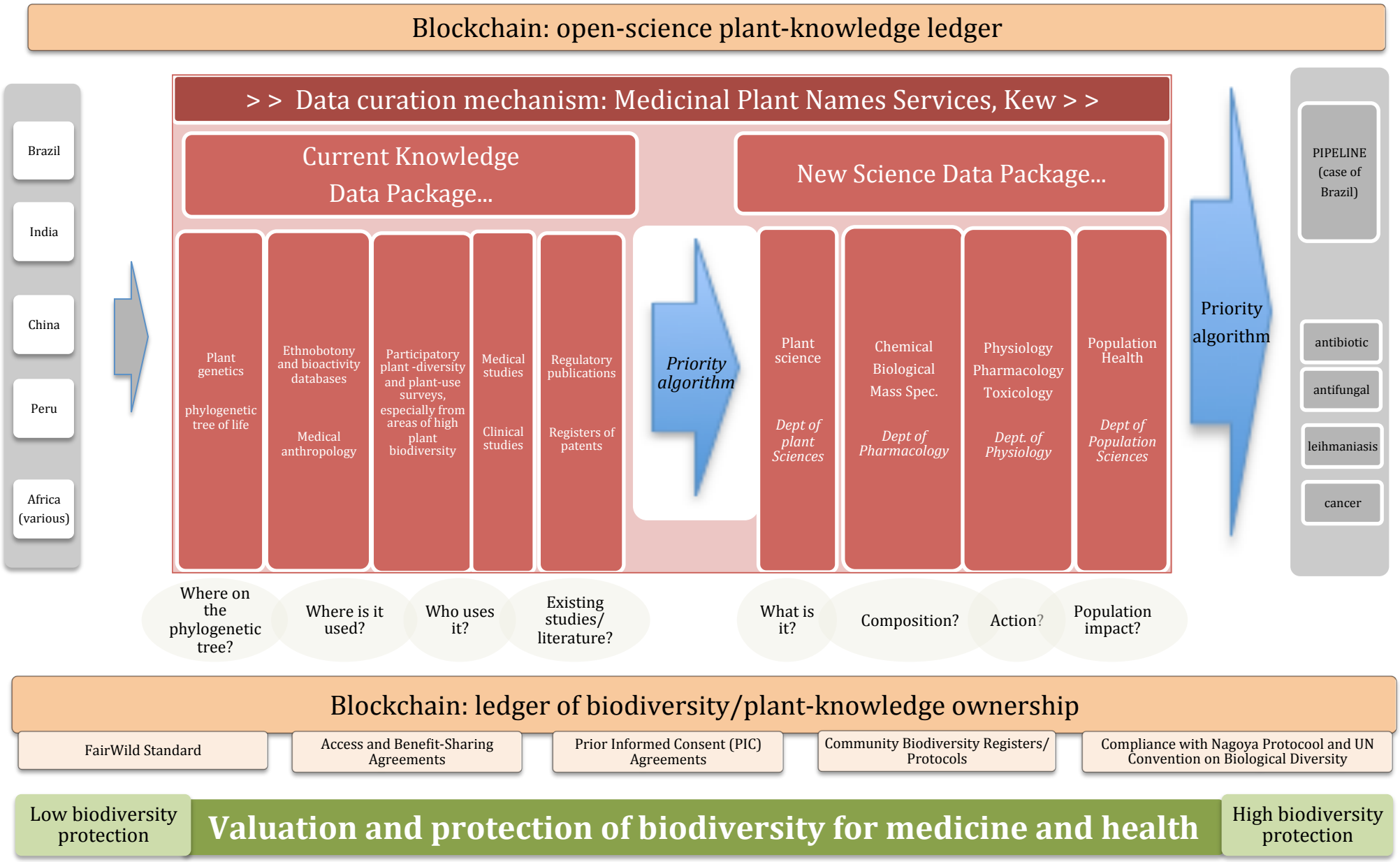
A multidisciplinary partnership:

Over time, the initial network of the partnership might grow to comprise: 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, Medicine, Law, Biochemistry, and various business school groups (blockchain, AI, major projects, etc.), the Big Data Institute and the Target

[11] Groups in Nepal and Peru have also expressed an interest in piloting some ideas.
[12] See final report at https://cordis.europa.eu/result/rcn/174322_en.html.
[13] See http://www.afox.ox.ac.uk/about.

Discovery Institute, Medical Anthropology, and Plant Sciences ;the Global Health Network; the Royal Botanic Gardens, Kew, England, including a new joint initiative between Kew and Columbia; trade and conservation agencies, including CITES and TRAFFIC-Action on Wildlife Trade; WIPO (a partner of Plants for Health); the European Association of Social Anthropology; European Citizen Science Association; the Museum fur Naturekund, Berlin; the Robert Koch Institute; CDC Africa and African Academy of Sciences; Chinese Academy of Sciences; Centre for Agriculture and Bioscience International (CABI); DNDi, and GARDP. 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.

This partnership will get its power from its extraordinary multidisciplinary coverage, which cannot be found in the usual pharmaceutical sector. Key components include, among others, biology, chemistry, ethnobotany, medical anthropology, genomics, clinical science, statistics, computer science, law, Intellectual Property (IP), block chain, economics, contract design, geography, public health, epidemiology, ecology, sociology, and medical ethics. This will enable it to provide a global public good that no commercial entity alone would be capable of providing.


Blockchain: open-science plant-knowledge ledger
Brazil
India
China
Peru
Africa (various)
> > Data curation mechanism: Medicinal Plant Names Services, Kew > >
Current Knowledge Data Package...
New Science Data Package...
Plant genetics
phylogenetic tree of life
Ethnobotony and bioactivity databases
Medical anthropology
Participatory plant -diversity and plant-use surveys, especially from areas of high plant biodiversity
Medical studies
Clinical studies
Regulatory publications
Registers of patents
Priority algorithm
Plant science
Dept of plant Sciences
Chemical Biological Mass Spec.
Dept of Pharmacology
Physiology Pharmacology Toxicology
Dept. of Physiology
Population Health
Dept of Population Sciences
Priority algorithm
PIPELINE (case of Brazil)
antibiotic
antifungal
leihmaniasis
cancer
Where on the phylogenetic tree?
Where is it used?
Who uses it?
Existing studies/ literature?
What is it?
Composition?
Action?
Population impact?
Blockchain: ledger of biodiversity/plant-knowledge ownership
FairWild Standard
Access and Benefit-Sharing Agreements
Prior Informed Consent (PIC) Agreements
Community Biodiversity Registers/ Protocols
Compliance with Nagoya Protocool and UN Convention on Biological Diversity
Low biodiversity protection
Valuation and protection of biodiversity for medicine and health
High biodiversity protection