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REVIEW

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Molecules from nature: Reconciling biodiversity conservation and global healthcare imperatives for sustainable use of medicinal plants and fungi

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Societal Impact Statement

Plants and fungi have provided, or inspired, key pharmaceuticals for global health challenges, including cancer, heart disease, dementia, and malaria, and are valued as traditional medicines worldwide. Global demand for medicinal plants and fungi has threatened certain species, contributing to biodiversity loss and depletion of natural resources that are important for the health of humanity. We consider the evolving role of plants and fungi in global healthcare as new challenges to human health and to biodiversity arise. We present current and emerging scientific approaches, to uncover and preserve nature-based health solutions for the future, through harmonization with biodiversity conservation strategies.

Summary

Non-communicable diseases, including cardiovascular disease, cancer, and diabetes, are the main causes of deaths globally, and communicable diseases such as malaria and tuberculosis affect billions of people. Plants and fungi have provided key pharmaceuticals in our armory against these global health challenges, while in some regions of the world, they continue to have a central role in healthcare systems as traditional medicines. Consequently, global demand for plants and fungi in healthcare has threatened certain medicinal species, and is a driving factor in biodiversity loss. Yet the future of therapeutics from nature is evolving. Scientific advances are enabling the untapped potential of the world's plants and fungi to be explored for their medicinal value, and to reveal other roles they may have for improving health and well-being; this demonstrates the value of natural capital as an incentive for biodiversity conservation. Emerging technologies also offer new hope for safeguarding essential medicines for the future, by revealing more sustainable solutions for sourcing key natural products. This review discusses recent developments and future approaches for the discovery of natural products as medicines, for health and well-being, and strategies to harmonize the therapeutic use of biodiversity with its proactive conservation through nature-based solutions.

KEYWORDS

biosynthetic pathways, drug discovery, herbal medicine, medicinal plants, pharmaceutical, phylogenetics, threatened species, well-being

1 | INTRODUCTION

Non-communicable diseases, including heart disease, stroke, cancer, diabetes, and chronic lung disease, are responsible for almost 70% of deaths globally (World Health Organization [WHO], 2016). In addition, deaths due to dementias have more than doubled between 2000 and 2016, making it the 5th leading cause of deaths worldwide in 2016 (WHO, 2019a). There are global programmes that aim to address these and other health challenges such as the WHO's Sustainable Development Goals (SDGs). SDG 3, to ensure healthy lives and promote well-being for all at all ages, aligns with the WHO's 13th General Programme of Work to achieve universal health coverage (UHC), address health emergencies, and promote healthier populations (WHO, 2019b). Despite some progress for SDG3 targets for particular communicable diseases, including global declines in HIV and tuberculosis (TB) incidence, TB is still a leading cause of ill health and death. Drug-resistant TB remains a threat, and progress in malaria control appears to have slowed (WHO, 2018a). TB and other potentially life-threatening bacterial infections occur against a backdrop of emerging antibiotic resistance (Woolhouse et al., 2016), which is an escalating threat to global health and food security. For these, and other diseases, drugs derived from plants and fungi are fundamental in our armory against global health challenges (Dauncey & Howes, 2020).

Plants and fungi have provided, or inspired, many pharmaceuticals (commonly referred to as drugs; Notes S1 and Table S1) in the WHO's Model List of Essential Medicines, including therapeutics for infections (e.g. artemether, penicillins), cancer (e.g. vincristine, etoposide), pain (e.g. aspirin, morphine), heart disease (e.g. digoxin, warfarin), and immunomodulation (e.g. ciclosporin) (WHO, 2019c). However, at least half of the world's population lacks full coverage of essential health services (WHO, 2020a) and traditional medicines, primarily prepared from plants, remain important for healthcare. Indeed, of the

estimated 350,000 vascular plant species known to science (WCVP, 2020), 7% (c. 26,000) have documented medicinal use (MPNS, 2020). Today, plants and fungi are embedded in global healthcare systems as sources of pharmaceuticals (Newman & Cragg, 2020a) or as traditional/complementary medicines, and are often associated with cultural and social significance (WHO, 2019d). It is therefore unsurprising that global demand for natural product medicines threatens the survival of certain species and is a driver of biodiversity loss.

Furthermore, many medicinal species are used by people in the region of origin, who have been their primary custodians and often hold unparalleled local knowledge. Scientists, governments, and other stakeholders must establish functional and equitable agreements to ensure that with respect to therapeutics from nature, there is compliance with the Nagoya Protocol and associated Access and Benefit Sharing legislation and consideration of the value and origins of any specimens collected (Pérez-Escobar et al., 2020).

It is not the intention of this review to discuss the efficacy and safety of natural products as medicines, or their impact on public health. Rather, we consider how the interactions between people, plants, and fungi have revealed new understanding of the role and preservation of natural resources for medicines, health, and well-being. We also discuss recent advances in natural product medicines discovery, and the role of plants and fungi in human health and well-being, particularly in the context of strategies to harmonize the therapeutic use of biodiversity with its proactive conservation through nature-based solutions.

2 | THE EVOLUTION AND CURRENT STATUS OF THERAPEUTICS FROM NATURE

2.1 | Global health challenges

Plants and fungi are the source of some of our most important drugs, including those so chemically complex (e.g. the anticancer drugs vincristine and vinblastine from the Madagascar periwinkle [*Catharanthus roseus* (L.) G.Don] (Howes, 2018)) that they may never have been discovered without natural product research. It has been suggested that prospecting nature to find new drugs is unnecessary because the number of different biological functions would not equate to the millions of chemically distinct natural molecules, and because ligands for specific molecular targets are likely to be found in many different species (Tulp & Bohlin, 2002). However, the remarkable chemical diversity of plants and fungi, and their impressive capability to synthesize highly complex novel compounds with 'drug-likeness' properties (Harvey, Edrada-Ebel, & Quinn, 2015; Jia, Li, Hao, & Yang, 2020; Koehn & Carter, 2005), provide substantial evidence that new drugs may still be discovered amongst the estimated 350,000 known vascular plant species, and estimated 2.2–3.8 million fungal species, many of which remain chemically unexplored (Dauncey & Howes, 2020; Harvey et al., 2015; 2017; Hawksworth & Lücking, 2017). Indeed, there has been some criticism from industry and academia of the focus on high-throughput screening of synthetic compounds for drug discovery, whilst natural products are regarded as yielding higher 'hit rates' (Amirkia & Heinrich, 2015).

Of 185 small molecule drugs approved for cancer (1981–2019), 65% were natural product derived or inspired (Newman & Cragg, 2020a). Recent advances in cancer therapeutics include the antileukaemia drug omacetaxine (homoharringtonine), originally from *Cephalotaxus* spp. (Cragg & Pezzuto, 2016; Howes, 2018), and ingenol mebutate, a topically-applied medicine for actinic keratosis, originally from milkweed (*Euphorbia peplus* L.) sap (Berman, 2012; Dauncey & Howes, 2020; Newman & Cragg, 2020a; Ogbourne & Parsons, 2014). These and other plant-derived drugs remain important in cancer therapeutics today (Howes, 2018). Yet the benefits to humanity of natural product derived drugs have not been without impact on biodiversity (Box 1).

Chronic obstructive pulmonary disease (COPD) is a leading cause of death globally (WHO, 2016); smoking and air pollution are contributing factors (WHO, 2020b). Pharmaceuticals derived from plant alkaloids are used to support smoking cessation, including nicotine originally from tobacco (*Nicotiana tabacum* L.) and varenicline, designed from the laburnum (*Laburnum anagyroides* Medik.) alkaloid, cytisine (Dauncey & Howes, 2020; Niaura, Jones, & Kirkpatrick, 2006). The Solanaceae alkaloid atropine was the basis for antimuscarinic drugs (e.g. tiotropium) for COPD (Moulton & Fryer, 2011). A 'green infrastructure' (urban vegetation) is predicted to improve urban air quality (Hewitt, Ashworth, & MacKenzie, 2020), with potential impact on human health, however, forests and certain plantations (e.g. oil palm [*Elaeis guineensis* Jacq.]) are the largest global emitters of biogenic volatile organic compounds (bVOCs), including monoterpenes and their precursor isoprenes, which can influence ground-level ozone formation. More research is needed to understand the complex interactions among bVOCs, ecosystems, and climatic factors, and the long-term effects on human health and well-being.

Two drugs specifically developed for dementia symptoms are derived from plant alkaloids: galantamine, originally discovered in snowdrop (*Galanthus woronowii* Losinsk.) bulbs, and rivastigmine, developed from physostigmine, an alkaloid from calabar beans (*Physostigma venenosum* Balf.) (Howes & Perry, 2011). Since 2002, every drug developed for Alzheimer's disease, the most common form of dementia, has failed in clinical trials (Crow, 2018), and those showing promise are unlikely to be sufficiently cost-effective for widespread clinical implementation in the foreseeable future. Despite some promising natural product drug candidates (Howes, 2013; Williams, Sorribas, & Howes, 2011), the urgent need remains to discover new strategies to prevent or delay dementia, including greater consideration of therapeutic and nutraceutical interventions. Certain plant oils may alleviate behavioral and psychological symptoms of dementia (e.g. agitation) and may also influence cognition, and benefit quality-of-life (Abuhamdah et al., 2008; Burns et al., 2011; Elliott et al., 2007; Huang et al., 2008; Okello & Howes, 2018; Press-Sandler, Freud, Volkov, Peleg, & Press, 2016). Emerging data suggest that particular dietary components or nutraceuticals may reduce or prevent cognitive decline (Howes, Perry, Vásquez-Londoño, & Perry, 2020), emphasizing the necessity for future research on how plants and fungi as medicines, nutraceuticals, or dietary components may benefit humanity by promoting healthy aging.

BOX 1 Drug discovery from *Taxus* spp.

Paclitaxel, originally from Pacific yew (*Taxus brevifolia* Nutt.) bark, was developed as an anticancer drug in the 1970s; thousands of trees were needed to obtain sufficient quantities for clinical use (Cragg & Pezzuto, 2016; Oberlies & Kroll, 2020). This contributed to a decline of around 30% in the populations within the last three generations, and the species is now Near Threatened (Thomas, 2013). Similarly, Asian yews *T. chinensis* (Pilg.) Rehder and *T. mairei* (Lemée & H.Lév.) S.Y.Hu have undergone significant population reductions as a result of their exploitation following paclitaxel discovery and are now Endangered and Vulnerable respectively (Thomas, Li, & Christian, 2020; Yang, Christian, & Li, 2013). In northwest India and western Nepal, exploitation led to a decline of up to 90% of *Taxus* populations, notably *T. contorta* Griff., which is also now Endangered (Thomas, 2011).

Knowledge embedded in taxonomy and chemistry enabled a more sustainable solution – precursor chemicals in the leaves and twigs of the common yew (*T. baccata* L.) were discovered, and could be used not only for semi-synthesis of paclitaxel, but also for the analogues docetaxel and cabazitaxel (Cragg & Pezzuto, 2016; Howes, 2018). Today, international policies (Williams et al., 2020) aim to protect biodiversity from such exploitation, but may also discourage research to discover new medicines that benefit humanity. Paclitaxel can be produced by plant cell cultures (Expósito et al., 2009) and in the future, paclitaxel yield could be further improved by synthetic biology applications. Although efforts to improve paclitaxel yields by heterologously expressing the biosynthetic pathway (Li et al., 2019) in other organisms are currently incomplete (all of the required genes are currently undetermined), such discoveries could provide new insights, strategies, and techniques to understand how paclitaxel is produced, paving the way to provide more sustainable sources of natural product medicines.

Taxus baccata L.

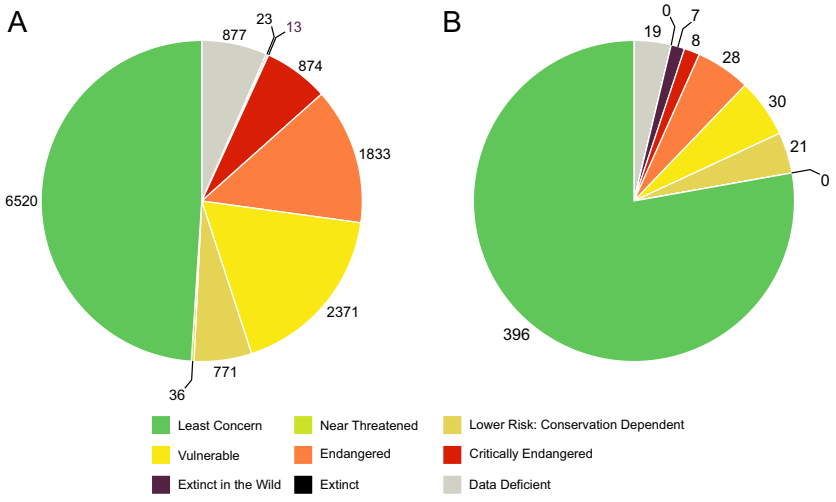
Photo credit: Dr Aljos Farjon

For diabetes, recent advances include the development of sodium-dependent glucose transporter (SGLT)-1/2 inhibitor drugs (e.g. sotagliflozin approved in the EU in 2019), based on the dihydrochalcone phloretin 2′-*O*-glucoside (Newman & Cragg, 2020a), which occurs in plants such as apples (*Malus domestica* (Suckow) Borkh.) (Simmonds & Howes, 2016). Other current strategies for prevention or management of diabetes and cardiovascular disease are underpinned by healthy diets (WHO, 2020c) to help prevent obesity and reduce disease risk (WHO, 2017, 2018b). Dietary approaches to address malnutrition, obesity and other health challenges must be aligned with strategies for food security (Ulian et al., 2020), and with research to understand the impact of climate change on the nutritional and medicinal value of plants and fungi, and the potential consequences for long-term human health (Borrell et al., 2020). The benefits of plants to human health may be even more extensive than simply providing medicines and a healthy diet; recent evidence links green spaces to positive effects on human health, including obesity reduction, improved mental health, mood and other indicators of well-being (Buck, 2016; Burton, 2014; Whear et al., 2014). With respect to public health, trees, and urban nature may promote health and social well-being by removing air pollution, reducing stress, encouraging physical activity, and promoting social ties and community (Turner-Skoff & Cavender, 2019).

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a major concern to human health and was subject to 1,253 patents between 1976 and 2010 (Oldham, Hall, & Forero, 2013). Some plant constituents (e.g. sophoradiol) are active against drug-resistant strains of *M. tuberculosis* and show additive effects with anti-TB pharmaceuticals (Lu et al., 2020). A promising area of research is

BOX 2 Medicinal Species in Latin America

In Latin America there is high plant biodiversity, such as in the Amazon rainforest, the Andean Mountains, and the Central American tropical and subtropical forests (Galvez-Ranilla, Kwon, Apostolidis, & Shetty, 2010). The use of medicinal plants generally increases with the species richness of the local flora (De la Torre, Cerón, Balslev, & Borchsenius, 2012), yet it is estimated that fewer than 25,000 plant species have been scientifically evaluated (Calixto, 2005). There are numerous threats to the long tradition of plant and fungal uses as medicines, foods, and in healing rituals (Bussmann & Sharon, 2006; Figure 1; Table S2); in 2019, the world witnessed destruction to the Amazon basin by fires (Borunda, 2020). Facing this situation, Latin American medicinal plant research needs to ensure impact in demonstrating the richness and potential of this natural resource to scientific and social sectors, whilst providing additional incentives to protect biodiversity.



Conservation status of (A) plants in Latin America and (B) medicinal plants in Latin America currently assessed according to global IUCN Red List Categories and Criteria.

Medicinal use is recorded for 509 of the 13,289 Latin American species assessed for their global conservation status (IUCN, 2020), although those species assessed may not be a representative sample, e.g. more than one in ten those species assessed are cacti, a family for which all known species have been assessed. Of medicinal flora of this region, 14% are Extinct/Extinct in the Wild/Threatened with Extinction, whereas 38% of the assessed Southern American flora are Extinct/Extinct in the Wild/Threatened with Extinction (see Figure above), which is consistent with the global pattern. Of the 280 fungi species currently assessed (IUCN, 2020), 38 occur in Latin America, yet none of these are recorded as medicinal.

the use of plants to produce vaccine antigens for TB; the secretory antigenic target (ESAT-6) in *M. tuberculosis* has been expressed in *Brassica cretica* Lam. via *Agrobacterium*-mediated transformation, inducing an immune response in vivo (Saba et al., 2020). This suggests that plants could be used as sources of low-cost agriculturally produced vaccines, while fungal leads for TB also show promise.

2.2 | Fungi as sources of pharmaceuticals

Since the serendipitous discovery of penicillin from *Penicillium rubens* Biourge, fungi have provided humans with important bioactive compounds, including the immunosuppressant ciclosporin, that allowed successful organ transplantation and the antihypercholesterolaemic statins (Hyde et al., 2019); and inspired drugs for Parkinson's disease (e.g. bromocriptine) (Dauncey & Howes, 2020), and for multiple sclerosis, such as fingolimod and its analogues (Newman & Cragg, 2020a). Since the twentieth century, prospecting fungal biodiversity has mostly been restricted to easy-to-grow soil moulds in high-throughput screens, which are not adapted to mimic the diverse conditions that trigger bioactive compound production (Keller, 2019). Genome analyses have identified an outstanding number of uncharacterized biosynthetic pathways in fungi (Kjærbølling et al., 2018; Nielsen et al., 2017), a largely untapped resource for drug discovery. Prospection of fungal biodiversity offers key advantages over plants: collecting fungi is not detrimental to ecosystems as only a minuscule portion of mycelium is sampled. It even facilitates preserving biodiversity because sampled fungal strains, if cultured in

laboratory conditions, can be conserved in biobanks in compliance with the Nagoya protocol and national legislation (Vu et al., 2019; Williams et al., 2020; CBD, 2020). Current prospection particularly focuses on endophytic (Newman & Cragg, 2020b) and *sensu stricto* marine fungi (Overy, Rämä, Oosterhuis, Walker, & Pang, 2019), but many other unexplored ecological niches deserve more interest, for example fungi associated with insects and arthropods.

Almost all clinically successful fungal-derived drugs possess some antimicrobial activity. Obvious examples include antibiotics (e.g. penicillins, cephalosporins); less obvious examples include ciclosporin and lovastatin, which are potent antifungals, although their medical applications are in non-antimicrobial therapeutic areas (Qiao, Kontoyiannis, Wan, Li, & Liu, 2007; Yang et al., 2018). Many other fungal-derived drugs have antimicrobial and additional bioactivities (Malani, 2019; Prince et al., 2013; Yam et al., 2018). Research in this field offers hope for the escalating urgency to discover new antibiotics to address emerging antimicrobial drug resistance. Indeed, the worryingly limited number of anti-TB agents has provided strong impetus for drug discovery, with fungi emerging as valuable sources of lead compounds; e.g. UT-800, which is derived from pleuromutilin, obtained from *Pleurotus mutilus* (Fr.) P.Kumm (Lemieux et al., 2018). Fungi yield many other compounds of interest for other diseases including diabetes, cancer, and certain viral infections (Hyde et al., 2019). Considering the urgency to address current and emerging health challenges such as the 2020 global coronavirus (COVID-19) pandemic, and the long time-scale needed to discover and develop new medicines, bioactive fungal (and indeed plant) compounds should be investigated as potential pharmaceuticals as part of longer term research strategies to provide a wider repertoire of genuine therapeutic options when health emergencies arise.

2.3 | Status of traditional and complementary medicines

Global use of herbal medicines – including herbal pharmaceuticals, dietary supplements, and functional foods – is booming. Expanding at a rate of about 6% per year, global sales may reach USD 130 billion by 2023; the largest component, herbal pharmaceuticals, generated about USD 51 billion of sales in 2017 (Marketwatch, 2019). Numerous factors drive growth, including the rising prevalence of chronic diseases, and the search for therapies where conventional ones are lacking. In Europe, including the UK, the status of herbal medicines with a 'well-established use' was harmonized by EU Directive 2004/24/EC, such that herbal medicinal products must have a long tradition of medicinal use (at least 30 years, including 15 years in the European Union), and must meet required standards for safety and quality; for the latter, products must comply with European or other relevant pharmacopoeia monographs, but there is no requirement for efficacy (European Parliament & Council of the European Union, 2004). Also in 2004, the United States Food and Drug Administration launched a 'botanicals' pipeline for drugs, which can include plant and fungal materials; to date, only two botanical drugs have been approved by this route: sinecatechins and crofelemer, from tea (*Camellia sinensis* (L.) Kuntze) and dragon's blood (*Croton lechleri* Müll.Arg.) respectively (FDA, 2016). In some regions of the world, plants and certain fungi are used as traditional medicines, but are often not formally regulated by legislation, yet the WHO aims to strengthen the role such medicines play in keeping populations healthy (WHO, 2013). These forms of traditional medicines usually contain mixtures of compounds, and are thus distinguished from pharmaceutical drugs containing a single active ingredient (Notes S1).

Historically, herbal medicines have played a central role in the health systems of countries where healthcare often involves a high proportion of out-of-pocket expenditure and recourse to private markets, including for medicines. For millions living in rural areas, traditional healers are their main health providers and source of medicines. The ratio of traditional healers to population in Africa is 80 times that of 'conventional' medical doctors, while up to 4 billion people worldwide rely on herbal medicines as a primary source of healthcare (Ekor, 2013; WHO, 2013). In China, herbal medicines represent about 40% of all healthcare services delivered (Ekor, 2013).

For a long time, the WHO paid little attention to herbal medicines. Recent global efforts to promote UHC in the face of rising healthcare costs and squeezed budgets, have prompted reassessment. Recognizing that 'conventional' pharmaceuticals are unaffordable and inaccessible in many places while herbal medicines are readily available, affordable, and culturally acceptable, has led the WHO toward integrating Traditional and Complementary Medicine (T&CM) into healthcare systems (WHO, 2013, 2019d). There is particular interest in the prevention and management of lifestyle-related chronic diseases, and in meeting the health needs of ageing populations. The WHO took steps to address challenges linked to the quality, efficacy, safety, and standardization of herbal medicines (see section 4.2), (WHO, 2013), pledging 'To support Member States in providing safe, qualified, and effective T&CM services and their appropriate integration into health systems for achieving UHC and the SDGs (Ghebreyesus, 2019). By 2018, 64% of all WHO Member States had implemented national regulations on herbal medicines, and 34 included traditional or herbal medicines in their National Essential Medicines Lists (medicines that satisfy the priority healthcare needs of the population) (WHO, 2019d). To illustrate these challenges, the main combination therapies for malaria are based on artemisinin (from *Artemisia annua* L.) or its derivatives to improve patient adherence and avoid acquired drug resistance; however, because there is a danger that uncontrolled use of artemisinin will encourage malaria-drug resistance, the WHO ruled not to support non-pharmaceutical forms (i.e. plant material) of *A. annua* for malaria (WHO, 2012).

The increasing coexistence of traditional and conventional 'scientific' approaches to medicine in healthcare systems is not yet mirrored in research and development efforts. Challenges include finding new ways to pool and rationally collate all available knowledge about the use and science of medicinal plants and fungi,

BOX 3 Medicinal Species in South Africa

South Africa ranks amongst the top countries worldwide in terms of frequency of medicinal plant use, with approximately 27 million individuals relying on traditional healthcare (Chen et al., 2016). A major concern is the overharvesting and unsustainable use of wild medicinal plants, resulting in biodiversity loss; e.g. *Encephalartos woodii* Sander is extinct in the wild (Mander, 1998; Van Wyk, Oudshoorn, & Gericke, 2013; Williams, Victor, & Crouch, 2013). The variation seen in numbers of species traded as medicinal plants between 1998 (700) and 2013 (350) may be due to reduced availability of plant species (Van Wyk & Prinsloo, 2018). Trade of bulbs, bark, and roots is particularly destructive, especially since plants are not replaced (Mander, 1998; Van Wyk et al., 2013); approximately 86% of harvested plant parts result in death of the plant (Mander, Ntuli, Diederichs, & Mavundla, 2007). Several South African medicinal plants are traded at traditional markets, and many are listed on the South African Red Data List as species of concern (Table S3).

South African government regulations and acts aim to control the overharvesting and biopiracy of indigenous biological resources. Examples include the National Environmental Management: Biodiversity Act 10 (2004), the National Biodiversity Strategy and Action Plan, and the National Biodiversity Framework, which all comply with the Convention on Biological Diversity. The National Environmental Management: Protected Areas Act 57 (2003) permits access to indigenous biological resources, if harvested sustainably. While there is a Traditional Health Practitioners Act 22 (2007), complementary/alternative medicines are not sufficiently regulated, which perhaps allows for overharvesting and exploitation of these resources (Street, Stirk, & Van Staden, 2008; van Wyk & Prinsloo, 2018).

Encephalartos woodii Sander

Photo credit: Royal Botanic Gardens, Kew

separating genuine efficacy from hearsay, and enabling the identification of potential new medicines. The global demand for naturally derived medicines also presents existential threats to some species.

3 | THREATENED MEDICINAL PLANTS AND FUNGI

Only six medicinal fungi are assessed on the global International Union for Conservation of Nature (IUCN) Red List of Threatened Species; of these, one is threatened: eburiko (*Fomitopsis officinalis* (Batsch) Bondartsev & Singer), now possibly extinct in Spain, while the Chinese caterpillar fungus (*Ophiocordyceps sinensis* (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones & Spatafora), a traditional Chinese medicine, is Vulnerable (IUCN, 2020). This highlights the importance of fungal biobanks and the need for their more systematic use to preserve fungal biodiversity. Many more medicinal plants have been assessed, reflecting the more extensive medicinal use of plants globally and the significant challenges in assessing fungi (Nic Lughadha et al., 2020). Of the 25,906 plant species with documented medicinal use (MPNS, 2020), all species that are not hybrids were analysed (WCVP, 2020), leaving 25,791 species remaining for analysis. Of these, 5,411 (21%) are represented by assessments on the IUCN Red List (IUCN, 2020). Of those assessed, 723 (13%) are categorized as threatened. Coverage of medicinal plants by IUCN Red List assessments is significantly higher than for plants with no

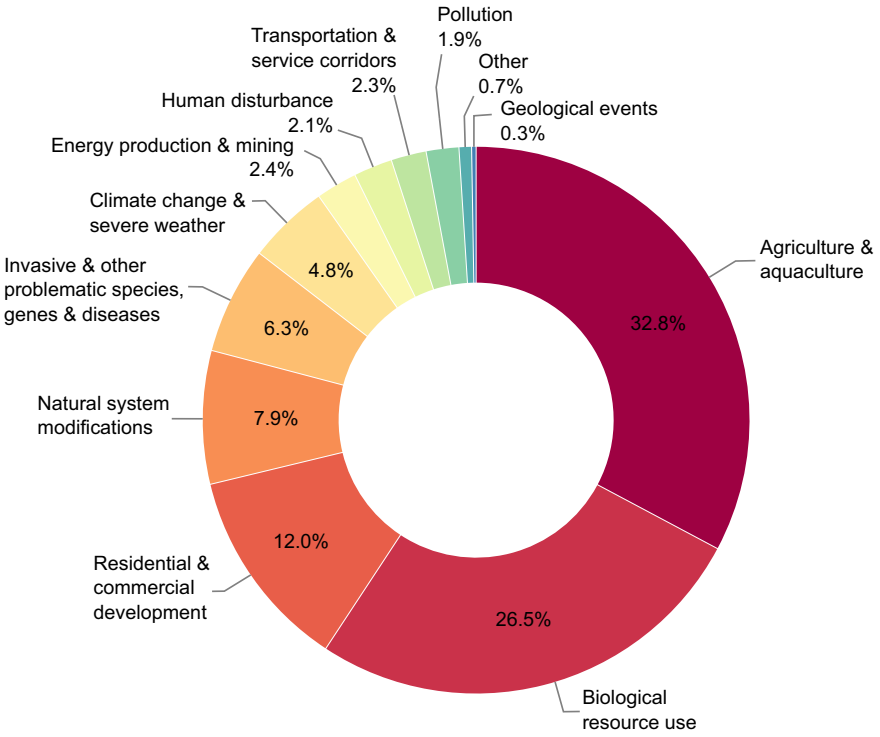


FIGURE 1 Threat spectrum showing relative importance of different threats reported for medicinal plant species that have global assessments on the IUCN Red List of Threatened Species (IUCN, 2020)

reported medicinal use ($Z = 54.3$, $p < .001$). Therefore, the odds of a species being assessed for the IUCN Red List more than doubles if that species is reported to be medicinal (2.44×, 95% CI = [2.36, 2.52]). This increased coverage of medicinal plants can be due in part to targeted efforts to assess medicinal plants and taxonomic groups sometimes considered to be rich in medicinal plants (e.g. Cactaceae) for the IUCN Red List (e.g. Allen et al., 2014; Goettsch et al., 2015).

On average, extinction risk to medicinal plants is lower than for plants with no reported medicinal use ($Z = -40.4$, $p < .001$). The odds of a species on the IUCN Red List being assessed as threatened are five times lower if the species is medicinal (0.187×, 95% CI = [0.172, 0.202]). When considering all digitally available global assessments using data from ThreatSearch (BGCI, 2020), and not only those published on the global IUCN Red List, the total rises to 10,673 medicinal species assessed (42%), but the overall patterns are broadly similar to those seen on the IUCN Red List (Notes S2).

Conservation risks associated with exploitation of certain medicinal species are well-documented (Figure 1), so the relatively low mean extinction risk to medicinal plants may seem surprising to the general reader. However, this low mean extinction risk is consistent with observations over two decades that 'weedy' and/or introduced species are over-represented in traditional medicinal floras, and that availability is a key factor in explaining this (Stepp & Moerman, 2001; Hart et al., 2017). Low mean extinction risk for medicinal plants is also consistent with the fact that weeds are over-represented among plants that are the sources of modern drugs (Stepp, 2004), and a more recent report notes that the likelihood of development of an alkaloid into a medicinal product is considerably influenced by the abundance of the source species (Amirkia & Heinrich, 2014). This latter finding also supports the view that access and supply constraints represent a key obstacle to the development of natural products by the pharmaceutical industry (Harvey, 2008).

Availability as a key factor in determining which plants are recognized to be useful as medicines goes beyond the consideration of weedy or introduced plants and is supported by our finding that, overall, medicinal plants tend to have larger native ranges than species not reported as medicinal ($W = 1.13 \times 10^9$, $p < .001$) (Notes S2). Since native range size is the strongest predictor of extinction risk in plants (Darrah, Bland, Bachman, Clubbe, & Trias-Blasi, 2017; Nic Lughadha et al., 2018), the relatively low mean extinction risk of medicinal plants is less surprising. Another factor, less easily quantified, is great human interest in medicinal plants (Petrovska, 2012), especially where plants are relied upon for primary healthcare (Barata et al., 2016). Heightened interest often results in exploitation, but it may also motivate sustainable management of these natural resources (Ghorbani, Langenberger, Liu, Wehner, & Sauerborn, 2012; Senkoro, Shackleton, Voeks, & Ribeiro, 2019; Terer, Muasya, Dahdouh-Guebas, Ndiritu, & Triest, 2012).

Research to enhance survival prospects of medicinal species is frequent in regions where primary healthcare relies on plants (Boxes 2–4). Plant conservation literature often focuses on plants known only from a single country (national endemics), and on species assessed as threatened. Medicinal plant conservation literature de-emphasizes plant endemism, often focusing on maintaining populations of medicinal plants within national borders, even if they thrive better elsewhere, with an emphasis on maintaining genetic diversity that is not explicitly captured by current

BOX 4 Medicinal Species in Ethiopia

Traditional plant remedies are important sources of therapeutics for nearly 80% of Ethiopians (Abebe & Ayehu, 1993), whilst about 95% of traditional medicine preparations in Ethiopia are plant-derived (Demissew & Dagne, 2001; Lulekal, 2018). In Ethiopia, 1,093 medicinal plants are documented, accounting for 18% of the country's flora, and about 3% of the medicinal plants are endemic (Esubalew, Belete, Lulekal, Gabriel, & Engidawork & E., Asres, E., 2017; Lulekal, 2018; Lulekal, Asfaw, Kelbessa, & Van Damme, 2012; Yineger, Kelbessa, Bekele, & Lulekal, 2008). Herbs (37%) represent the dominant form of Ethiopian medicinal plants, followed by shrubs (35%), trees (22%), and climbers (4%) (Lulekal, 2018).

About 80% of Ethiopian medicinal plants are harvested from the wild (29% for their root), with serious conservation implications (Lulekal, 2018). Medicinal plant harvest was reported as 56,000 tonnes per annum (Mander, Emana, Asfaw, & Busa, 2006). The most commonly sold Ethiopian medicinal plants include *Hagenia abyssinica* (Bruce) J.F.Gmel., *Embelia schimperi* Vatke, *Ximenia americana* L., *Jatropha curcas* L. and *Tamarindus indica* L. (Lulekal, 2018; Mander et al., 2006). There is comparatively poor documentation of Ethiopian medicinal fungi. Those described in the few Ethiopian ethnomycological documents include *Termitomyces microcarpus* (Berk. & Broome) R.Heim, *T. clypeatus* R.Heim and *Laetiporus sulphureus* (Bull.) Murrill (Woldegiorgis et al., 2015). Despite their value for healthcare and the economy, Ethiopian medicinal plants and fungi are subject to loss due to anthropogenic and environmental factors (Lulekal, 2018; Lulekal et al., 2012; Stévart et al., 2019). Future strategies to conserve this biodiversity could include promoting documentation of medicinal species and associated indigenous knowledge, *in situ* and *ex situ* conservation, and promotion of scientific research.

Tamarindus indica L.

Photo credit: Dr Gwilym P. Lewis

extinction risk classifications (Rivers, Brummit, Nic Lughadha, & Meagher, 2014). Such steps may enhance the continued supply of valuable medicinal compounds, and may reduce biodiversity loss since species not considered Threatened or Near Threatened facing a high risk of extinction in the wild under global IUCN Red List criteria may nonetheless be of conservation concern, and attract research and timely conservation intervention. Indeed, one in five of the Chinese medicinal plants considered highest priority for conservation are not assessed to be threatened following IUCN Red List criteria (Huang, Zhang, & Qin, 2020; Notes S3; Figure S1).

4 | FUTURE DIRECTIONS TO HARNESS DISCOVERY, WELL-BEING AND CONSERVATION

4.1 | Predicting medicinal species

A fundamental, but often overlooked, obstacle complicates the use and conservation of medicinal plants: there are too many names applied to these plants and many of these names are ambiguous, employed inconsistently through time and across different geographies (Dauncey, Irving, Allkin, & Robinson, 2016). The complexity and inconsistency in

BOX 5 Plant-based malaria therapeutics

Identification of new plant-based malaria therapeutics may be facilitated by phylogenetic approaches. These identify 'hot zones', such as Cinchoneae (Rubiaceae) and Rauvolfioideae (Apocynaceae), based on existing knowledge, thus focusing on potential active compounds. Some of these genera in the antimalarial 'hot zones', do not occur in malaria regions [e.g. *Skytanthus* (Apocynaceae)] (Flora do Brasil, 2020), so are not known by local people as potential malaria remedies (De Albuquerque et al., 2004; Silva et al., 2011). This makes it difficult to predict the impact of species loss on medicines, and therefore, health. As a result, many species will likely be lost before we know their potential medicinal value (Zhu et al., 2011).

The number of plants that have medicinal uses is under-estimated, due to the lack of ethnobotanical publications for some regions (Souza & Hawkins, 2017). Over 60 species used for malaria in Latin America are not cited at all in the published scientific literature, their use being documented only on herbarium specimen labels (William Milliken, unpublished data). Of the species used for malaria in Latin America, 32% are assessed on the IUCN Red List and 48% on ThreatSearch; of these, 6% and 7%, respectively, are threatened, principally due to agriculture and logging.

Protecting locally threatened medicinal plants and fungi in areas where they are used may be more important than focusing on globally threatened species. This means considering plant habitats and their protection, rather than individual species. The Important Plant Areas criteria developed at Kew has incorporated culturally important species into site-based conservation prioritization (Darbyshire et al., 2017). Similarly, in malaria therapeutics, better collaboration between modern and traditional systems is also required (Willcox, 2011).

Meanwhile, for malaria prophylaxis, the saponin QS-21 from the soap bark tree (*Quillaja saponaria* Molina) is being developed as a vaccine adjuvant (Didierlaurent et al., 2017).

Cinchona pubescens Vahl bark

Photo credit: Laura Green/Royal Botanic Gardens, Kew

the use of these names bedevils regulation, research, and attempts to count or analyse trends statistically (Allkin et al., 2017). Harmonization of medicinal plant (Allkin et al., 2017; MPNS, 2020) and fungal terminologies will be fundamental to track past research, and to predict which plants and fungi will be important medicinally.

Large phylogenetic projects [e.g. Plant and Fungal Trees of Life (RBG Kew, 2020)] will enhance the ability to predict which plants and fungi potentially share chemical pathways, and thus have similar medicinal properties. Rapid growth in available genetic data enables the development of an increasingly detailed picture of the

phylogenetic distribution of medicinal species. Far from being randomly distributed across the plant tree of life, genera containing traditionally used medicinal species show clustered patterns, which are also evident in the species from which clinically approved drugs are derived (Ernst et al., 2016; Pellicer et al., 2018; Saslis-Lagoudakis et al., 2012; Zhu et al., 2011). The phylogenetic clustering of species with medicinal uses has been explored in South American palms in which species with medicinal uses as a whole do not show phylogenetic clustering, while five of the seven different subcategories investigated show strong phylogenetic clustering (Cámara-Leret et al., 2017). Furthermore, community phylogenetic approaches to disentangle the potential drivers of similarity between different ethnofloras show that related plants from widely separated regions are often used for medicinal conditions in the same therapeutic areas (Saslis-Lagoudakis et al., 2012). These results, and the concentration of bioactive compounds within the clades highlighted, represent strong evidence to independently reveal medicinally useful species, and thus for the potential of ethnobotanical datasets to inform bioprospecting.

Phylogenetic approaches at species and infraspecific levels also offer great potential for identifying the most appropriate sources for specific therapeutic molecules (Box 5). Bioprospecting in a phylogenetic context can also help identify appropriate alternatives to medicinal species under pressure from exploitation, but the fact that species known for their medicinal use tend to have large native ranges should be considered to avoid transferring pressures from them to more range-restricted species that may be intrinsically more susceptible to extinction. For example, the cytotoxic and anti-tumor activities of *Paris forrestii* (Takht.) H.Li have led to it being a suggested substitute for its larger-ranged but over-exploited congener *P. polyphylla* var. *yunnanensis* (Franch.) Hand.-Mazz. in traditional Chinese medicine (Wang et al., 2018). Although categorized as Least Concern on the global IUCN Red List (Chadburn, 2017), *P. forrestii* is assessed as Endangered within China (MEP & CAS, 2013; Qin et al., 2017). Nonetheless, its cultivation on a large scale is a factor that deems it an appropriate substitute (Wang et al., 2018). Phylogenetic analysis at the level of individuals and subpopulations within a single species may help pinpoint the factors determining chemical diversity within species, and thus accelerate discovery of medicines. In *Cinchona calisaya* Wedd., the most productive source of the antimalarial quinine, chemical diversity between individuals has been demonstrated to be primarily driven by phylogeny (Maldonado et al., 2017).

4.2 | Future approaches for natural products as therapeutics

Advances in high-throughput screening, combinatorial chemistry, and molecular biology, and shifts in therapeutic strategies underpinned by the development of biological agents, combined with necessary legislation to protect biodiversity, have together contributed to a decline in natural product drug discovery in recent decades (Harvey et al., 2015; Howes, 2018). Today, the role of plants and fungi in the development of medicines extends beyond revealing new active small molecules; their role in medicine is evolving. Drug repurposing is one approach, where drugs licensed for one therapeutic application are evaluated for their potential usefulness for others; for example, aspirin, originally based on salicylates from willow bark (*Salix* spp.) (Oketch-Rabah, Marles, Jordan, & Low Dog, 2019) is an analgesic, anti-inflammatory, antipyretic, and anti-platelet drug, but it is now of interest for use in cancer therapeutics (Antoszczak, Markowska, Markowska, & Huczyński, 2020).

Naturally derived compounds used in pharmaceutical manufacture include shikimic acid, sourced from star anise (*Illicium verum* Hook.f.), a precursor for semi-synthesis of the anti-influenza drug, oseltamivir (Patra et al., 2020). Future manufacturing of medicines could harness other plant and fungal molecules as precursors for drug synthesis to complement other therapeutic strategies for current and emerging global health challenges, such as the 2020 coronavirus (COVID-19) pandemic. Furthermore, in 2003, traditional herbal medicines were used to help manage and contain severe acute respiratory syndrome (SARS; another coronavirus) in China (Tilburt & Kaptchuk, 2008), although more studies are needed to further evaluate their observed effects, due to methodological issues with the clinical trials in which Chinese herbal medicines were evaluated for efficacy in SARS (Leung, 2007; Liu, Manheimer, Shi, & Gluud, 2004). In this context, the role of traditional medicines in global health challenges merits greater scrutiny, including their chemistry, pharmacology, authentication, safety, and efficacy, with the latter evaluated in controlled clinical trials, to the level of standards comparable to those for pharmaceutical drugs.

The 'waste' or untapped potential of plants and fungi currently used in non-medical industries, could also yield rewards through provision of other molecules for medicines manufacture, and thus could contribute to SDG12 for sustainable management and efficient use of natural resources. A notable example is sisal (*Agave sisalana* Perrine): its leaves are a source of fiber used in the textile industry, yet the remaining waste is a source of steroidal compounds (e.g. hecogenin) which provides the starting material for producing around 5% of global steroids for the pharmaceutical industry (Dauncey & Howes, 2020), making use of this natural resource more efficient.

5 | ADVANCES IN RESEARCH TECHNOLOGY: HARMONIZATION FOR HUMANITY AND BIODIVERSITY

5.1 | Discovering molecules from nature

Limitations in analytical chemistry and computing technologies required for dereplication of complex plant and fungal extracts (to eliminate compounds previously studied) have been barriers for drug discovery. Recent advances are resulting in striking changes. Community-wide contributions to data annotation (Wang

et al., 2016) enable rapid identification and discovery of natural products. Dereplication through molecular networking has emerged as such a means for rapid compound identification in complex mixtures through visualization of tandem mass spectra (MS/MS) data; the largest repository and data analysis tool for this approach is the Global Natural Products Social Molecular Networking (GNPS) (Quinn et al., 2017; Wang et al., 2016). Advances in mass spectrometry (MS) imaging, such as matrix assisted laser desorption ionization (MALDI-MS), desorption electrospray ionization (DESI-MSI), and laser ablation electrospray ionization (LAESI-MS) have expanded capabilities for *in situ* analyses of samples (Jarmusch & Cooks, 2014). Furthermore, applications of a droplet probe coupled to ultraperformance liquid chromatography-photodiode array-high resolution tandem mass spectrometry (UPLC-PDA-HRMS/MS) has enabled chromatographic separation of micro-extracts derived from herbarium specimens without damaging them (Kao, Henkin, Soejarto, Kinghorn, & Oberlies, 2018).

Advances in nuclear magnetic resonance (NMR) spectroscopy include the Metabolomics and Dereplication by Two-dimensional Experiments (MADByTE) tool, which leverages heteronuclear single quantum coherence (HSQC) spectroscopy and total correlated spectroscopy (TOCSY) data to construct spin systems of a compound, and uses these features to generate association networks for analyses (Egan & Linington, 2019). In addition to applications of these new analytical techniques in drug discovery initiatives, exploration of plant metabolite diversity has also proven useful to phylogenetic and evolutionary studies within genera and across larger groups of angiosperms (Ernst et al., 2019; Henz Ryen & Backlund, 2019). Beyond advances in mass spectrometry and nuclear magnetic resonance, emerging technologies that unite the strengths of X-ray crystallography with electron microscopy are enabling crystal structures of tiny quantities of certain natural products in mixtures to be determined. A recent application of electron cryo-microscopy and microcrystal electron diffraction demonstrated the utility of this technique in structural determination of heterogeneous mixtures of natural products (Jones et al., 2018). Leveraging this and other advancing chemical technologies offers great potential to obtain rapid analytical data from small (<1 mg) samples.

Never before have plant and fungal natural products been more accessible for scientific study. Government funded science agencies are availing their resources to scientific partners for investigation; e.g., the USA's National Cancer Institute (NCI) Program for Natural Product Discovery Prefractionated Library includes over 150,000 fractions of natural products available to scientists (Thornburg et al., 2018). This library integrates biodiversity breadth and chemical diversity, with the full collection covered by existing ethical bioprospecting agreements. Combined with better access to taxonomically diverse collections of plants and fungi (Paton et al., 2020), large chemical repositories of natural products, and robust ethical guidance for cultural data and plant genetic resources, these recent advances in analytical chemistry could support finding new chemical blueprints for drug development across many fields of medicine.

5.2 | Advances in the biosynthetic pathways of medicinal molecules

The elucidation of biosynthetic pathways, combined with engineered fungal/plant/bacterial cell factories, offer new strategies to produce bioactive compounds while preserving biodiversity. Linking biosynthetic genes to bioactive molecules is now possible, due to an increasing number of available genomes and transcriptomes, and the use of heterologous hosts (e.g. *Aspergillus oryzae* (Ahlb.) Cohn and yeast: *Saccharomyces cerevisiae* Meyen ex E.C. Hansen) (Harvey et al., 2018; Skellam, 2019). Such a strategy is commonly used in fundamental research and is promising for large-scale industrial production (Hyde et al., 2019; Steiniger et al., 2017).

Genomic and biotechnological advances make fungal fermentation-based processes ideal to produce bioactive compounds from fungi and plants (Pyne, Narcross, & Martin, 2019). Yeast cell factories enable production of medicinally valuable plant alkaloids (Galanie et al., 2015; Srinivasan & Smolke, 2019), steroids (Rieck et al., 2019), and coumarins (Zhao et al., 2019). A successful example of this approach is the heterologous expression of the precursor artemisinic acid in yeast, with yields appropriate for industrial-scale production; it can be converted to the antimalarial artemisinin using a chemical source of singlet oxygen (Paddon et al., 2013). Similarly in yeast, biosynthesis of the opium alkaloid cough suppressant noscapine was reconstructed using over 30 genes from plants, bacteria, mammals and fungi (Li et al., 2018). Combining biosynthetic genes from different pathways in the same fungal host has also successfully produced new compounds with different or enhanced activities (Srinivasan & Smolke, 2019; Steiniger et al., 2017). Global demand for the herbal medicine rhodiola (*Rhodiola rosea* L.) and its compound salidroside, has resulted in this species and some varieties being threatened (BGCI, 2020). Elucidation of the salidroside biosynthetic pathway enabled its heterologous production in yeast and tobacco plants, offering future sustainable salidroside production (Torrens-Spence, Pluskal, Li, Carballo, & Weng, 2018). These examples illustrate the power of synthetic approaches to reconstruct biosynthetic pathways of bioactive compounds, with potential to reduce exploitation of natural resources. While engineered yeast has been used to produce bioactive compounds, the use of filamentous fungi such as *Aspergillus* species may be more promising as these fungi are already good secondary metabolite producers and they can accommodate genes from different organisms in order to produce compounds of interest (Frandsen et al., 2018). Mosses are also being developed as 'cell factories' for the production of plant compounds, with the obvious advantage of being more closely related to vascular plants (Reski, Parsons, & Decker, 2015).

Plant biosynthetic pathways for specialized metabolites are usually long and highly branched; their regulation is controlled by multiple regulatory elements, which are often poorly understood. Recent elucidation of the vinblastine pathway (Caputi et al., 2018; Qu et al., 2018; Tatsis et al., 2017) resulted in a paradigm shift in understanding specialized metabolism. Based on this example, the metabolic pathways of other indole alkaloids have been elucidated, including ibogaine (Farrow et al., 2018, 2019) from iboga

(*Tabernanthe iboga* Baill.), which has been studied for its effects on drug addiction (Dauncey & Howes, 2020), and the antiarrhythmic ajmaline (Dang et al., 2018; Dang, Franke, Tatsis, & O'Connor, 2017) from snakeroot (*Rauvolfia serpentina* (L.) Benth. ex Kurz). These studies lay new foundations for future developments in synthetic biology applications, especially to uncover metabolic pathways for medicinallScy important indole alkaloids such as the antimalarial quinine.

Himalayan mayapple (*Podophyllum hexandrum* Royle) contains higher levels of podophyllotoxin than the American mayapple (*P. peltatum* L.) so is the preferred source of this lignan for semi-synthesis of anticancer drugs (e.g. etoposide) (Howes, 2018). However, trade in *P. hexandrum* is restricted (CITES, 2019) because wild populations are under threat. Elucidation of the genes responsible for podophyllotoxin biosynthesis and reconstitution of the metabolic pathway in *Nicotiana benthamiana* Domin. opens new horizons for sustainable production in plants (Lau & Sattely, 2015; Schultz et al., 2019) or fungi. Production of bioactive compounds in engineered fungal strains is very appealing for sustainability and safety. The use of engineered food-grade fungi (e.g. *Aspergillus oryzae*) addresses the issue of wild-type fungi producing hazardous mycotoxins during fermentation (Marič et al., 2019). Producing new bioactive compounds in fungal 'cell factories' still requires significant efforts to become more widespread and economically viable. One key challenge is to develop tools to allow accurate prediction of biosynthetic pathways and enzyme specificities. A more cost-effective approach could also be to integrate this knowledge into semi-synthesis strategies that combine precursors produced by fermentation with chemical modifications (Sandargo et al., 2019).

6 | CONCLUSION

The future of therapeutics from nature is evolving as new challenges to human health and to biodiversity arise. Scientific evaluation of plants and fungi for their medicinal or other uses can demonstrate their value, providing additional incentives to protect global natural capital. In 2019, 1,955 and 1,886 new species of plants and fungi, respectively, were reported (Cheek, 2020); some may yield compounds useful to humanity (Cheek et al., 2018). Despite these discoveries, and the success of natural product drug discovery to provide essential pharmaceuticals, the full potential of the world's biodiversity remains heavily underexplored in the search for new medicines, and in the formation of strategies for our health and well-being. Advances in science and technology provide future opportunities to discover new molecules from nature, a plethora of metabolic pathways for their synthesis, and more sustainable ways to source them, underpinning potential solutions for global health challenges. These strategies, using biodiversity for inspiration, provide hope for increasing yields and safeguarding supplies of valuable medicines in the future.

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AUTHOR CONTRIBUTIONS

M-J.R.H. planned the review content, carried out literature research, wrote content included in all sections of the review, and edited the manuscript; E.N.L. also edited the manuscript. E.N.L., C.Q., J.C., E.T., D.T., E.L., A.F., L.P.L., M.-E.C., D.J.L., T.A.K.P., W.M., C.M., M.DeC., N.L., H.N.Q., C.V., B.A., M.R., and M.S.J.S. contributed written content on different topics included in key sections for the review. B.W. analysed data and developed Figures for the review. E.B. and B.A. checked and updated the plant names in the manuscript. A.B. and J.F. provided content for the Supporting Information and helped with formatting the References; C.L. also provided content for the Supporting Information. F.F. and C.W. provided expert comments on the phylogenetics and policy sections of the manuscript respectively.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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