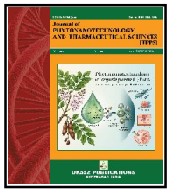
Journal of Phytonanotechnology and Pharmaceutical Sciences 6(3): 25-32, 2026

Online ISSN:2583-0376

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.54085/jpps.2026.6.3.3

Journal of Phytonanotechnology and Pharmaceutical Sciences



Review Article : Open Access

Forest biodiversity as a reservoir of novel therapeutic compounds: Opportunities for drug discovery and development

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Article Info

Article history

Received 8 August 2026

Revised 10 September 2026

Accepted 11 September 2026

Published Online 30 September 2026

Keywords

Forest biodiversity

Bioprospecting

Secondary metabolites

Endophytes

Ethnopharmacology

Drug discovery

Sustainable utilisation

Abstract

Forests cover about one-third of the terrestrial surface and harbour the majority of known land-based species, making them the largest natural repository of chemical diversity on Earth. Plants, fungi, lichens, bacteria and endophytic microbes inhabiting forest ecosystems have evolved an immense array of secondary metabolites in response to intense biotic and abiotic pressures, and many of these molecules have become the foundation of modern medicine, including paclitaxel, camptothecin, the vinca alkaloids, quinine and reserpine. Despite this record, only a small fraction of forest species has been examined comprehensively for bioactivity, and forest loss, over-harvesting and climate change are eroding this resource faster than it can be explored. This review summarises the ecological basis of chemical diversity in forests, highlights the taxonomic groups that serve as reservoirs of therapeutic compounds, and discusses the role of ethnobotanical knowledge in guiding discovery, with special reference to biodiversity-rich regions such as the Western Ghats of India. Modern enabling technologies, including metabolomics, molecular networking, genome mining, synthetic biology, network pharmacology and cheminformatics, are examined for their ability to accelerate lead identification and to relieve supply bottlenecks. Key barriers such as sustainable sourcing, standardisation, compound interference, and access and benefit-sharing obligations are discussed, and an integrated framework linking conservation with drug discovery and development is proposed.

1. Introduction

Natural products have provided humanity with medicines for millennia and remain central to contemporary pharmacotherapy (Dias *et al*., 2012). An analysis of new drug approvals over nearly four decades showed that natural products, their derivatives and compounds inspired by their pharmacophores account for a substantial share of approved small-molecule drugs, and for more than half of the agents introduced in oncology and anti-infective therapy (Newman and Cragg, 2016; Newman and Cragg, 2020). The structural complexity, stereochemical richness and evolutionary pre-validation of natural molecules allow them to occupy regions of chemical space that are poorly covered by synthetic libraries (Clardy and Walsh, 2004; Patridge *et al*., 2016). Although, interest in natural products declined in the pharmaceutical industry during the era of combinatorial chemistry and high-throughput screening, advances in analytical chemistry, genomics and computational science have led to a renewed appreciation of their value (Li and Vederas, 2009; Harvey *et al*., 2015; Atanasov *et al*., 2021).

Forests are the principal arena in which this chemical diversity is generated. According to the Global Forest Resources Assessment, forests occupy about 4.06 billion hectares, or roughly 31% of the global land area (FAO, 2020). They contain a very large proportion of terrestrial species, yet current estimates suggest that millions of eukaryotic species remain undescribed (Mora *et al*., 2011). Of the roughly 350,000 to 400,000 known vascular plants, more than 28,000 have a documented medicinal use (Allkin, 2017), and a much smaller number has been investigated rigorously for phytochemistry, mechanism of action and clinical efficacy (Kinghorn *et al*., 2011). Fungi, lichens, soil bacteria and the microbial communities living inside plant tissues add further layers of unexplored chemistry.

The importance of this reservoir is increasingly set against a background of ecological loss. Global tree cover declined by millions of square kilometres in the first decade and a half of this century (Hansen *et al*., 2013), and species are presently disappearing at rates far above the background rate (Pimm *et al*., 2014). Each extinction removes not only an organism but also a unique set of biosynthetic pathways and, often, the associated traditional knowledge. An early economic analysis argued that the value of pharmaceuticals yet to be discovered in tropical forests alone provides a strong argument for their conservation (Mendelsohn and Balick, 1995). The link between biodiversity and drug discovery is therefore both scientific and ethical: protecting forests protects future therapeutic options.

The present review brings together current knowledge on forest biodiversity as a source of novel therapeutic compounds. It describes the ecological drivers of chemical diversity, catalogues the major biological sources and notable forest-derived drugs, discusses the contribution of traditional knowledge, evaluates modern technologies that are reshaping the discovery pipeline, and examines the scientific,

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supply-related and legal challenges. Finally, it outlines strategies by which forest-based drug discovery and development can proceed in a sustainable and equitable manner.

2. Forest biodiversity and the origin of chemical diversity

2.1 Global forest biodiversity and hotspots

Forest biomes range from boreal coniferous belts to tropical rainforests, and from dry deciduous woodlands and montane cloud forests to mangroves. Tropical moist forests are the most species-rich of these, whereas temperate and boreal forests contribute distinctive lineages such as conifers, which provided the taxanes. Forests also function as a major carbon sink and regulate regional climate, so that their degradation has consequences well beyond biodiversity loss (Pan *et al*., 2011). Conservation planning has long relied on the concept of biodiversity hotspots, regions with exceptional endemism that have lost most of their original vegetation. Of the 25 hotspots originally recognised, several are forest-dominated and include the Western Ghats and Sri Lanka, Indo-Burma, the tropical Andes, Madagascar and the Atlantic forests of Brazil (Myers *et al*., 2000). These areas coincide with the origin of many important medicines: quinine from the Andean cinchona forests, vinca alkaloids from Madagascar, and reserpine from the forests of the Indian subcontinent.

2.2 Ecological drivers of secondary metabolite diversity

Secondary metabolites are not essential for basic growth but mediate interactions with the environment, including defence against herbivores and pathogens, protection from ultraviolet radiation, allelopathy, signalling and attraction of pollinators and seed dispersers (Wink, 2003). Their structural diversity is thought to arise from an evolutionary arms race in which organisms continuously modify existing biosynthetic scaffolds to overcome the resistance of attackers. Because many of the target proteins of these molecules, such as ion channels, receptors, enzymes and cytoskeletal components, are conserved between insects, microbes and mammals, defensive compounds frequently show pharmacological activity in humans (Wink, 2015).

Several features of forest ecosystems intensify this chemical evolution. Tropical forests experience high herbivore and pathogen pressure throughout the year, and long-lived, slow-growing plants in resource-poor soils tend to invest heavily in costly chemical defences (Coley *et al*., 1985; Coley and Barone, 1996). Vertical stratification, from the forest floor to the canopy, creates numerous micro-habitats that support specialised epiphytes, lichens and microbial communities. In addition, intraspecific variation in metabolite profiles, shaped by genotype, soil, altitude, light and herbivory, produces distinct chemotypes within one species (Moore *et al*., 2014). This variation has practical significance: the concentration of the active principle in a given plant may differ markedly with the provenance and season of collection, which in turn influences both discovery and quality control.

3. Forest-derived drugs and drug leads

The historical record shows that forest species have contributed prominently to the pharmacopoeia. Table 1 lists a selection of drugs and leads that originated from forest-associated organisms, together with their therapeutic relevance.

Table 1: Selected drugs and leads derived from forest-associated organisms

Compound	Forest source	Therapeutic relevance	References
Paclitaxel	*Taxus brevifolia* Nutt. (Pacific yew); semi-synthesis from *Taxus baccata* L.	Microtubule stabiliser; ovarian, breast and lung cancers	Wani *et al*., 1971; Denis *et al*., 1988
Camptothecin (topotecan, irinotecan)	*Camptotheca acuminata* Decne.	Topoisomerase I inhibitors; colorectal, ovarian and lung cancers	Wall *et al*., 1966
Vinblastine, vincristine	*Catharanthus roseus* L. (Madagascar)	Antimitotic; leukaemias, lymphomas	Noble, 1990
Etoposide, teniposide	*Podophyllum* spp. (podophyllotoxin)	Topoisomerase II poisons; lung and testicular cancers	Hande, 1998
Combretastatin A-4	*Combretum caffrum* (Eckl. and Zeyh.) Kuntze.	Tubulin binder; vascular-disrupting lead	Pettit *et al*., 1989
Quinine	*Cinchona* spp. (Andean forests)	Antimalarial	Achan *et al*., 2011
Reserpine	*Rauvolfia serpentina* (L.) Benth. ex Kurz.	Antihypertensive; antipsychotic	Vakil, 1949
Huperzine A	*Huperzia serrata* (Thunb.) Trevis.).	Acetylcholinesterase inhibitor; Alzheimer's disease lead	Wang *et al*., 2006
Forskolin	*Coleus forskohlii* (Willd.) Briq..	Adenylate cyclase activator; research tool and lead	Ammon and Müller, 1985
Calanolide A	*Calophyllum lanigerum* Miq.	Anti-HIV non-nucleoside reverse transcriptase inhibitor lead	Kashman *et al*., 1992
Prostratin	*Homalanthus nutans* (G.Forst.) Guill..	Anti-HIV; latency-reversing lead	Gustafson *et al*., 1992
Betulinic acid	Woody plants (*e.g*., *Ziziphus*, *Betula*)	Selective cytotoxicity against melanoma cells	Pisha *et al*., 1995

Paclitaxel is perhaps the most instructive example. It was obtained from the bark of the Pacific yew, *T. brevifolia*, a slow-growing understorey tree of old-growth forests of the Pacific Northwest, and its structure was reported in the early 1970s (Wani *et al*., 1971). The compound stabilises microtubules and arrests cells in mitosis, which underlies its efficacy against ovarian, breast and lung cancers (Weaver, 2014). Because bark harvesting killed the trees and supply was extremely limited, the clinical development of the drug nearly stalled. The problem was solved by semi-synthesis from 10-deacetylbaccatin III, a precursor that can be obtained from the renewable needles of the European yew, *Taxus baccata* (Denis *et al*., 1988), and later by plant cell culture fermentation (Frense, 2007). The paclitaxel story thus illustrates both the promise of forest biodiversity and the supply and sustainability issues that must be anticipated early in development.

Camptothecin, a quinoline alkaloid isolated from the Chinese tree *C. acuminata* (Wall *et al*., 1966), inhibits DNA topoisomerase I and has yielded the clinically used analogues topotecan and irinotecan. The vinca alkaloids vinblastine and vincristine, obtained from the Madagascar periwinkle *C. roseus*, were identified during an investigation of a plant used traditionally for diabetes and became cornerstones of the treatment of leukaemia, lymphoma and other cancers (Noble, 1990). Etoposide and teniposide are semi-synthetic glycosides of podophyllotoxin, a lignan from *Podophyllum* species of forest understorey, and act as topoisomerase II poisons (Hande, 1998). Combretastatin A-4, a stilbene from the South African bushwillow *C. caffrum*, binds tubulin and disrupts tumour vasculature, and its phosphate prodrug has been evaluated extensively in clinical trials (Pettit *et al*., 1989). Overall, natural products and their derivatives continue to form a major portion of the anticancer armamentarium (Cragg *et al*., 2009).

Forest-derived antimalarials have had a similar effect. Quinine, from the bark of *Cinchona* species native to Andean montane forests, remained the mainstay of malaria therapy for centuries and still has a role in severe disease (Achan *et al*., 2011). Artemisinin, discovered through a systematic screening of traditional Chinese remedies, transformed malaria treatment and earned a Nobel Prize for its discoverer (Tu, 2011). Although, *Artemisia annua* is not a forest species, the discovery demonstrates how traditional knowledge can direct researchers towards a pharmacologically active plant.

Other examples extend the therapeutic range. Reserpine from *R. serpentina*, a shrub of the moist deciduous forests of India, was among the first effective antihypertensive and antipsychotic agents (Vakil, 1949). Huperzine A, a reversible acetylcholinesterase inhibitor from the clubmoss *H. serrata*, has been studied for Alzheimer's disease (Wang *et al*., 2006), while galantamine, a related alkaloid first investigated from the snowdrop on the basis of local Caucasian folk use, is an approved treatment for mild to moderate dementia (Heinrich and Teoh, 2004). Forskolin, a labdane diterpene from *C. forskohlii* used in Ayurvedic medicine, activates adenylate cyclase and became an indispensable pharmacological tool (Ammon and Müller, 1985). Within antiviral research, the coumarin calanolide A from the Sarawak rainforest tree *C. lanigerum* (Kashman *et al*., 1992) and prostratin from the Samoan tree *H. nutans* (Gustafson *et al*., 1992) have been explored as anti-HIV leads, and betulinic acid, a lupane triterpenoid found in many woody plants, was reported as a selective inducer of apoptosis in melanoma cells (Pisha *et al*., 1995).

4. Taxonomic reservoirs of therapeutic compounds

4.1 Higher plants

Higher plants remain the best-studied reservoir. Forest trees, shrubs, lianas, herbs and epiphytes produce alkaloids, terpenoids, polyphenols, flavonoids, coumarins, lignans, saponins and many other classes. Woody plants in particular accumulate large pools of structurally complex terpenoids and phenolics in bark, heartwood, resins and latex, which are rarely encountered in annual crops. Nonetheless, the great majority of forest plants has been screened only against a narrow set of targets, and many tropical species have never been subjected to full phytochemical investigation (Kinghorn *et al*., 2011). Rare and endemic plants of understudied regions therefore represent a particularly valuable but fragile opportunity.

4.2 Endophytic fungi and bacteria

Endophytes are microorganisms that live within plant tissues without causing disease symptoms. Forest plants host rich communities of such organisms, many of which synthesise bioactive metabolites, including antibiotics, antifungals, immunosuppressants, cytotoxins and antioxidants (Strobel and Daisy, 2003; Gunatilaka, 2006). The discovery of a taxol-producing endophytic fungus, *Taxomyces andreanae*, from the Pacific yew raised the prospect that microbial fermentation could replace plant extraction (Stierle *et al*., 1993), and endophytes from *C. acuminata* were later reported to produce camptothecin and its analogues (Kusari *et al*., 2009). Subsequent work, however, showed that production by many endophytes declines or is lost upon repeated subculture, a phenomenon attributed to the silencing of biosynthetic gene clusters outside the host environment and possibly to differences in the chemical ecology of the symbiosis (Kusari *et al*., 2012). Endophytes thus remain attractive, but claims of plant-compound production should be supported by rigorous isotopic and genetic evidence, and the stability of production must be demonstrated before they can be considered viable manufacturing platforms.

4.3 Macrofungi and medicinal mushrooms

Forest floors, decaying wood and living trees support an enormous diversity of macrofungi. Species such as *Ganoderma*, *Lentinula*, *Trametes*, *Inonotus* and *Cordyceps* produce polysaccharides, polysaccharide-protein complexes, triterpenoids and phenolics with immunomodulatory, antitumour and antiviral properties (Wasser, 2002; Lindequist *et al*., 2005). Fungi were also the source of the statins, the cholesterol-lowering drugs that originated from metabolites of *Penicillium* and *Aspergillus* species (Endo, 2010), demonstrating that fungal metabolites can generate blockbuster medicines. The standardisation of mushroom preparations and the chemical definition of the active fractions, however, remain important concerns.

4.4 Soil bacteria, lichens and the wider microbiome

Forest soils and leaf litter contain bacterial communities in which actinomycetes and other taxa carry large numbers of biosynthetic gene clusters, the majority of which are silent under standard laboratory conditions. Culture-independent sequencing of environmental DNA has revealed a vast, geographically structured reservoir of secondary metabolism that remains largely untapped (Charlop-Powers *et al*., 2015). Lichens, symbioses between fungi and algae or cyanobacteria, grow abundantly on tree trunks and rocks in humid forests and yield depsides, depsidones and usnic acid

derivatives with antimicrobial and cytotoxic activity. Together, these groups broaden the scope of forest bioprospecting beyond plants and offer chemical scaffolds that are especially relevant to the problem of antimicrobial resistance.

5. Traditional knowledge and ethnopharmacology as guides to discovery

Indigenous and local communities have accumulated detailed knowledge on the use of forest species through generations of observation. The ethnobotanical approach, which uses this information to prioritise species for study, has been recognised as an efficient route to new drugs (Cox and Balick, 1994). In a widely cited analysis, Fabricant and Farnsworth (2001) reported that about 80% of the plant-derived drugs they examined had a current therapeutic use that was the same as, or related to, the ethnomedical use of the source plant. Traditional knowledge therefore enriches the probability of finding activity compared with random collection, and it also contains information on preparation, dosage and safety that is of great practical value (Cordell and Colvard, 2012). The World Health Organization has acknowledged that large numbers of people in developing countries depend on traditional medicine for primary health care and has urged its safe and evidence-based integration into health systems (WHO, 2013).

India offers a compelling illustration. The country contains four of the global biodiversity hotspots or portions thereof, and its forests support hundreds of tribal communities with deep medicinal traditions across Ayurveda, Siddha, Unani and folk systems. An assessment of the demand and supply of medicinal plants in India documented that roughly 960 species are traded, with nearly 180 species consumed in quantities exceeding 100 metric tonnes per year, a large proportion being still collected from wild sources (Ved and Goraya, 2008). The case of *Trichopus zeylanicus*, known as arogyapacha, is particularly well known. Its use as an anti-fatigue food by the Kani tribe of the Western Ghats was documented in early ethnomedical studies (Pushpangadan and Atal, 1984) and led to the development of a polyherbal formulation, the licensing of which included a mechanism for sharing benefits with the Kani community. This example is often cited as a pioneering model of benefit-sharing, even though its long-term implementation has also been discussed critically (Laird and Wynberg, 2008).

Traditional knowledge is also adaptive ecological knowledge. Local communities manage harvest rotations, sacred groves and seasonal restrictions that often conserve the very species of interest (Berkes *et al*., 2000). Collaborative research designs that include communities as partners, respect prior informed consent and recognise intellectual contribution are therefore not only ethically necessary but scientifically productive, since they improve the quality of the ethnobotanical data and the long-term availability of plant material.

6. Therapeutic areas with high potential

Forest-derived compounds are being pursued across a broad spectrum of diseases. In oncology, natural scaffolds continue to supply tubulin binders, topoisomerase inhibitors, epigenetic modulators and agents that target apoptosis and angiogenesis (Cragg *et al*., 2009; Cragg and Newman, 2013). In infectious diseases, the growing crisis of antimicrobial resistance has stimulated renewed searches for antibacterial and antifungal molecules from endophytes, soil bacteria and lichens, while forest plants remain important sources of antimalarial, antiviral and anthelmintic leads. Neurodegenerative disorders constitute another focus, with cholinesterase inhibitors, neuroprotective polyphenols, and modulators of protein aggregation and neuroinflammation deriving from forest species (Wang *et al*., 2006). Metabolic and cardiovascular diseases, inflammatory conditions and pain are further areas in which forest plants, long used in folk medicine, are being subjected to modern pharmacological evaluation. Table 2 presents the main therapeutic areas together with representative source groups and the types of molecular targets involved.

Table 2: Therapeutic areas and representative forest-derived sources

Therapeutic area	Representative source groups	Typical molecular targets	References
Cancer	Woody plants, understorey herbs, endophytic fungi, mangrove trees	Tubulin, topoisomerases, apoptotic regulators, angiogenesis pathways	Cragg *et al*., 2009
Infectious diseases	Endophytes, soil actinomycetes, lichens, medicinal trees	Cell wall synthesis, protein synthesis, viral enzymes, parasite metabolism	Strobel and Daisy, 2003; Achan *et al*., 2011
Neurodegeneration	Clubmosses, bulbous plants, poly-phenol-rich trees	Cholinesterases, amyloid and tau aggregation, neuroinflammation	Wang *et al*., 2006
Cardiometabolic disorders	Forest shrubs, medicinal mushrooms, fungal metabolites	HMG-CoA reductase, adrenergic and vascular targets, glucose metabolism	Endo, 2010; Vakil, 1949
Inflammation and immunity	Medicinal mushrooms, resin-bearing trees, lichens	NF-kB, cyclooxygenases, cytokine signalling, immune receptors	Wasser, 2002; Lindequist *et al*., 2005

7. Modern technologies for accelerating forest bioprospecting

The classical workflow of collecting a plant, preparing extracts, performing bioassay-guided fractionation and isolating an active compound is slow and often rediscovers known molecules. Recent technological developments are changing this approach by allowing the chemistry of complex biological samples to be read at scale and by providing access to compounds without depending on the original organism (Beutler, 2009; Wolfender *et al*., 2019). The principal approaches are summarised in Table 3.

7.1 Metabolomics, dereplication and molecular networking

High-resolution liquid chromatography-mass spectrometry combined with nuclear magnetic resonance spectroscopy allows thousands of metabolites in an extract to be profiled in a single experiment. Dereplication, the rapid recognition of known compounds, avoids

the repeated isolation of previously described molecules and thereby saves considerable effort (Gaudêncio and Pereira, 2015). Tandem mass spectrometry data can be organised into molecular networks that group structurally related compounds, as implemented in the Global Natural Products Social Molecular Networking platform (Wang *et al*., 2006) and its feature-based extension (Nothias *et al*., 2020). When such data are combined with bioactivity measurements, it is possible to prioritise extracts and individual features that are both novel and active, before any isolation is attempted. Open compound databases now compile hundreds of thousands of natural product structures and assist in the annotation of unknown peaks (Sorokina and Steinbeck, 2020).

Table 3: Modern approaches that support forest-based drug discovery

Approach	Contribution to discovery	Representative examples
LC-MS/NMR metabolomics and dereplication	Early recognition of known compounds; prioritisation of novel chemistry	Gaudêncio and Pereira, 2015; Wolfender *et al*., 2019
Molecular networking	Visualises related metabolites and links them to bioactivity	GNPS and feature-based networking
Genome mining	Detects cryptic biosynthetic gene clusters in plants and microbes	antiSMASH; environmental DNA surveys
Synthetic biology and metabolic engineering	Sustainable heterologous production of scarce molecules	Artemisinic acid and opioid biosynthesis in yeast
Network pharmacology and AI	Models multi-target actions; prioritises species and extracts	Hopkins, 2008; natural product databases
Semi-synthesis and plant cell culture	Renewable supply from abundant precursors or cell lines	Paclitaxel production

7.2 Genome mining and synthetic biology

Sequencing of plant, fungal and bacterial genomes has shown that organisms carry far more biosynthetic gene clusters than the number of metabolites observed under laboratory conditions. Bioinformatic tools such as antiSMASH identify and classify these clusters, and thereby guide the activation of cryptic pathways or their heterologous expression (Blin *et al*., 2021). Synthetic biology can also solve supply problems. The best-known example is the engineering of *Saccharomyces cerevisiae* to produce artemisinic acid, which is converted chemically to artemisinin (Ro *et al*., 2006). Similarly, the complete biosynthesis of opioids in yeast has been achieved by assembling more than twenty enzymes from plants, bacteria and rodents (Galanie *et al*., 2015). These achievements demonstrate that complex forest-derived molecules can eventually be produced in fermenters, which reduces pressure on wild populations. For many pathways in woody and tropical species, however, the genes are still unknown, and the elucidation of complete plant pathways remains a major scientific challenge.

7.3 Network pharmacology, cheminformatics and artificial intelligence

Crude extracts typically act through multiple compounds on multiple targets. Network pharmacology offers a framework to model such polypharmacology by representing compounds, targets and diseases as interacting networks (Hopkins, 2008), and it is increasingly used to generate hypotheses on traditional formulations. Machine learning models trained on natural product databases can predict targets, bioactivity and ADMET properties, and can prioritise taxa or extracts likely to contain new chemotypes. Retrospective analysis of discovery trends suggests that the rate of rediscovery can be reduced through such data-driven prioritisation (Pye *et al*., 2017). The reliability of these tools nevertheless depends on the quality, diversity and annotation of the training data, and computational predictions must be validated experimentally.

8. Challenges in forest-based drug discovery and development

8.1 Supply and sustainability

Many forest-derived leads are present in very low concentrations in slow-growing species. Harvesting wild populations for medicinal use can accelerate their decline, and overexploitation is a leading threat to many medicinal plants (Schippmann *et al*., 2002; Hamilton, 2004). Chen *et al*. (2016) emphasised that conservation and sustainable use of medicinal plants require coordinated efforts including in situ and ex situ conservation, domestication, cultivation, and the development of alternative sources. Early evaluation of supply options such as renewable plant parts, semi-synthesis, total synthesis, tissue culture and microbial production should accompany hit identification, so that a promising molecule does not become a clinical candidate that cannot be manufactured, as nearly occurred with paclitaxel.

8.2 Chemical and pharmacological complexity

Natural extracts are complex mixtures, and the isolation, structure elucidation and chemical synthesis of new molecules is demanding. Variability in the metabolite profile with season, geography and processing creates difficulties in standardisation and reproducibility (Moore *et al*., 2014). Constituents may interact synergistically or antagonistically, so that the activity of the extract cannot always be reconstructed from the isolated components (Caesar and Cech, 2019). In addition, some natural compounds, such as polyphenols, quinones and catechols, behave as pan-assay interference compounds that give false positives in screening assays through aggregation, redox cycling or covalent reactivity (Baell and Holloway, 2010). Careful assay design, orthogonal validation and early assessment of selectivity, pharmacokinetics and toxicity are needed to avoid pursuing artefacts. Many natural products also suffer from poor bioavailability and chemical instability, which may demand formulation or medicinal chemistry optimisation.

8.3 Legal, ethical and intellectual property aspects

The Convention on Biological Diversity affirmed national sovereignty over genetic resources and established the principle of fair and equitable sharing of benefits arising from their use. The Nagoya Protocol, in force since 2014, strengthened these obligations by requiring prior informed consent and mutually agreed terms for access to genetic resources and associated traditional knowledge (CBD, 2011). The uncertainty and administrative burden created by access regulations were reported to reduce natural product research in some sectors (Cragg *et al*., 2012), whereas well-designed partnerships between providers and users have been shown to deliver tangible benefits (Laird and Wynberg, 2008). Researchers must therefore plan for permits, material transfer agreements, benefit-sharing arrangements, documentation of traditional knowledge and appropriate patent strategies from the start of a project.

8.4 Regulatory pathways and clinical translation

Single-compound drugs follow the standard regulatory route for new chemical entities, whereas standardised extracts, botanical drugs and traditional formulations require quality specifications, proof of batch consistency and, increasingly, clinical evidence. Insufficient chemical characterisation of preparations and weak trial design have been persistent causes of irreproducible herbal research. Harmonisation of quality standards, pharmacovigilance for herbal products and investment in well-designed clinical studies are necessary to move forest-derived therapeutics from tradition to evidence-based medicine.

9. Future perspectives and an integrated strategy

The future of forest-based drug discovery lies in the integration of conservation, community partnership and technology. Several priorities can be identified. First, systematic inventories and biodiversity databases should be linked with chemical and ecological information, so that sampling can target phylogenetically distinct, ecologically stressed and under-explored lineages in hotspots, including understudied taxa such as lianas, epiphytes and cryptogams. Second, voucher specimens, taxonomic authentication and metadata on locality, season and habitat must accompany every sample to ensure reproducibility. Third, the full discovery pipeline, from metabolomics-guided prioritisation to genome-informed biosynthetic engineering, should be applied to extracts and microbial libraries, with sustainable supply addressed from the earliest stage (Kingston, 2011; Atanasov *et al*., 2021).

Fourth, community-based approaches are needed in which forest-dwelling communities are partners in research, share in benefits, and are supported in the cultivation and value-added processing of medicinal species, which diminishes pressure on wild populations while generating livelihoods. Fifth, national and international policies should link bioprospecting revenue to forest protection, thereby giving conservation a direct economic rationale that was already anticipated in early valuation studies (Mendelsohn and Balick, 1995). Sixth, training and capacity-building in biodiversity-rich countries, including India, should be strengthened so that discovery, development and value capture occur close to the source of the genetic resource. Taken together, these measures can convert forests from a repository that is being depleted into a renewable and equitably managed source of medicines.

10. Conclusion

Forests are an unparalleled reservoir of chemical diversity that has already given the world some of its most valuable medicines, including anticancer, antimalarial, antihypertensive and neuroactive agents. The ecological forces acting in forest ecosystems continue to generate novel scaffolds in plants, fungi, lichens and microbes, and traditional knowledge supplies a rational guide for selecting the species most likely to be useful. Contemporary tools such as metabolomics, molecular networking, genome mining, synthetic biology and computational modelling can overcome many of the historic obstacles of rediscovery, low yield and unsustainable harvesting. The principal constraints are now less technical than institutional: the loss of habitat, the lack of sustainable supply planning, insufficient standardisation, and the need for fair benefit-sharing. Drug discovery from forests will succeed in the long term only if it is pursued together with the conservation of the forests themselves and with respect for the people who have safeguarded them. Protecting forest biodiversity is therefore not merely an environmental objective but an investment in future human health.

Acknowledgements

The authors express their gratitude and credit the researchers behind the original studies whose works are referenced in this review.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

S. Umesh Kanna: Conceptualization, academic oversight, critical review and validation of scientific content; **H. B. Roghan**: Data curation.

Consent for publication

All authors gave full consent for publication and submission to this journal.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest relevant to this article.

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Citation **S. Umesh Kanna and H. B. Roghan (2026). Forest biodiversity as a reservoir of novel therapeutic compounds: Opportunities for drug discovery and development. J. Phytonanotech. Pharmaceut. Sci., 6(3):25-32, http://dx.doi.org/10.54085/ap.2026.6.3.3.**