Bioprospecting the Past a Comprehensive Review of Molecular Validation and Therapeutic Potential in Ancient Medical Traditions

Pragati Ranjan Satpathy*[1], Madhuchhanda Mishra[2], Jagannath Prasad Mishra[3], Kedar Behera[4]
[1,2,] *Associate Professor, Department of Pharmaceutical Analysis, Sri Jayadev College of Pharmaceutical Sciences, Naharakanta, Bhubaneswar, Odisha, India, 752101*
[3]*Assistant Professor, Department of Pharmaceutics, IMT Pharmacy College, Puri, Odisha, India, 752001*
[4]*Associate Professor, Department of Pharmaceutics, Sri Jayadev College of Pharmaceutical Sciences, Naharakanta, Bhubaneswar, Odisha, India, 752101*

Abstract- The declining efficiency of conventional drug discovery, as exemplified by Eroom's Law, has prompted renewed interest in ethnopharmacology as a scientifically credible and evolutionarily informed discovery paradigm. Ethnopharmacology integrates indigenous medical knowledge with Reverse Pharmacology, leveraging centuries of empirical human use to guide molecular validation and therapeutic translation. Unlike reductionist, single-target strategies that frequently fail against complex diseases, traditional medicinal systems employ chemically diverse, multi-component formulations capable of modulating interconnected biological networks.This review critically examines the renaissance of ethnopharmacology through systematic literature mapping, bibliometric network analysis, and standardized quality assessment frameworks, including PRISMA-Ethnopharmacology, ConPhyMP guidelines, and clinical rigor metrics. Ethnobotanical scaffolds—such as alkaloids, terpenoids, and polyphenols—are highlighted for their stereochemical complexity, intrinsic bioavailability, and capacity for poly-target engagement. Network pharmacology and systems biology approaches reveal that these natural products exert quantifiable synergistic effects by convergently regulating key signaling hubs, including NF-κB, PI3K/Akt/mTOR, AMPK, autophagy–lysosome pathways, and neuroplastic circuits.The relevance of ethnopharmacology is further underscored by global challenges such as antimicrobial resistance, metabolic disorders, cancer, and neurodegeneration, where single-node pharmacological interventions have proven inadequate. Traditional polyherbal formulations demonstrate enhanced therapeutic resilience by simultaneously targeting multiple disease-relevant pathways, thereby reducing resistance development and improving translational success. Ethical considerations, including compliance with the Nagoya Protocol and equitable benefit-sharing with indigenous knowledge holders, are emphasized as integral to responsible bioprospecting and commercialization.By synthesizing indigenous medical wisdom with modern analytical platforms, artificial intelligence, and omics technologies, ethnopharmacology is positioned at the forefront of Precision Ethnomedicine. This integrative framework offers a structurally diverse, ethically grounded, and biologically robust foundation for the discovery of next-generation therapeutics capable of addressing multifactorial and treatment-resistant diseases.

Key Words: Ethnopharmacology, Reverse Pharmacology, Network Pharmacology, Natural Product Drug Discovery, Poly-Target Therapeutics, Precision Ethnomedicine.

I. INTRODUCTION

Ethnopharmacology at the Interface of Indigenous Knowledge and Reverse Pharmacology

The renewed global interest in ethnopharmacology reflects a fundamental re-evaluation of contemporary drug discovery strategies. Positioned at the confluence of indigenous medical wisdom and Reverse Pharmacology, modern ethnopharmacology seeks to translate centuries of empirical bedside observations into mechanistically validated, bench-side therapeutics. This paradigm shift has gained urgency in light of Eroom's Law, which documents the steady decline in pharmaceutical R&D productivity despite unprecedented financial investment. The repeated failure of reductionist, target-driven

approachesparticularly those relying on chemically narrow synthetic librarieshas exposed intrinsic weaknesses in the “one target–one drug” doctrine when applied to complex biological systems.

In contrast, ethnobotanical remedies occupy a pre-validated chemical landscape, refined through prolonged human use across generations. Natural products derived from medicinal plants have effectively undergone informal clinical selection, resulting in higher translational success rates (approximately 0.1–1%) compared with random high-throughput screening (HTS) outputs. This enhanced performance is attributed to the presence of privileged molecular scaffolds, such as alkaloids, terpenoids, and polyphenols, which exhibit evolutionary compatibility with biological macromolecules. These scaffolds are characterized by stereochemical richness, favorable membrane permeability, and inherent multi-target activity, enabling functional synergy within interconnected signaling networks.

Beyond methodological innovation, the contemporary resurgence of ethnopharmacology raises critical ethical considerations. As bioprospecting accelerates toward commercial exploitation, the risk of biopiracy necessitates strict adherence to the Nagoya Protocol, ensuring equitable access, benefit-sharing, and recognition of indigenous communities as intellectual contributors rather than passive resource providers. Ethical governance, therefore, constitutes an essential pillar of scientifically responsible ethnopharmacological research.

The relevance of ethnopharmacology is further heightened by the onset of the post-antibiotic era, wherein antimicrobial resistance (AMR) has compromised the long-term utility of many single-target agents. Traditional polyherbal formulationssuch as *Artemisia*-based antimalarial therapies and berberine-containing botanical combinationsdemonstrate superior therapeutic resilience by concurrently disrupting bacterial efflux systems, cell wall biosynthesis, and metabolic adaptability. Such multi-node pharmacological interventions consistently outperform synthetic “magic bullets,” which are prone to rapid resistance development.

Beyond infectious diseases, ethnopharmacological strategies are increasingly informing therapeutic innovation in metabolic disorders and neurodegenerative conditions. Classical medical systems emphasize systemic rebalancing rather than isolated symptom suppression. Emerging molecular evidence indicates that several traditional bioactives can activate the autophagy–lysosome pathway (ALP), facilitating the clearance of neurotoxic aggregates such as amyloid-β and taupathological targets that have largely resisted conventional synthetic inhibitors. By decoding the inherent poly-pharmacology of traditional remedies through molecular and systems biology frameworks, ethnopharmacology offers an evolutionarily informed, structurally diverse pharmacopeia capable of addressing multifactorial diseases.

II. METHODOLOGY

Evidence-Based Frameworks for Ethnopharmacological Validation

To ensure methodological rigor and reproducibility, this review adopts a multi-layered validation strategy integrating systematic literature mapping, bibliometric analysis, and standardized quality assessment tools. This framework moves beyond anecdotal documentation and enables critical, evidence-driven appraisal of ethnopharmacological candidates.

Systematic Literature Mapping: PRISMA–Ethnopharmacology

A modified PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol was employed to guide study selection and ensure transparency.

- Identification: Comprehensive searches were conducted across PubMed, Scopus, Web of Science, and the Cochrane Library, supplemented by grey literature from ethnobotanical databases and classical pharmacopeial sources (e.g., Ayurvedic Pharmacopoeia, Materia Medica).
- Screening: Duplicate records and non-peer-reviewed reports lacking geographical, cultural, or historical coherence were excluded.
- Eligibility: Full-text articles were assessed using Reverse Pharmacology principles, prioritizing formulations with documented human use and clinical relevance.

- Inclusion: Only studies providing robust phytochemical characterization, pharmacological evaluation, and mechanistic insight were included.

Taxonomic authentication was mandatory, requiring accurate Latin binomial nomenclature supported by voucher specimens deposited in accredited herbaria.

Bibliometric Mapping: VOSviewer Analysis (1990–2026)

To capture the intellectual trajectory of ethnopharmacology, a keyword co-occurrence analysis was conducted using VOSviewer, encompassing publications from 1990 to 2026. Three major developmental phases were identified:

1. Documentation Phase (1990–2005): Dominated by ethnobotanical surveys, taxonomic studies, and cultural preservation efforts aimed at safeguarding rapidly disappearing traditional knowledge.
2. Screening Phase (2006–2018): Characterized by bioactivity-guided fractionation, in vitro pharmacological assays, and anti-inflammatory and antimicrobial screening.
3. Systems Pharmacology Phase (2019–2026): Marked by network pharmacology, metabolomics, synergy modeling, and investigations into the gut–brain axis, reflecting a shift toward holistic, systems-level analysis.

Quality Assessment Metrics

Clinical Rigor: Jadad Scale

Human intervention studies were evaluated using the Jadad scoring system, which assesses randomization, blinding, and participant accountability. Studies achieving scores ≥3 were considered methodologically reliable.

Phytochemical Transparency: ConPhyMP Guidelines

The ConPhyMP (Consensus-based Phytochemical Characterization of Medicinal Plant Extracts) protocol was applied to ensure extract reproducibility and chemical clarity, requiring:

1. Verified botanical identification and extraction methodology
2. Comprehensive chemical fingerprinting (HPLC, GC–MS, or NMR)
3. Contaminant and safety profiling

III. THE GLOBAL ETHNOPHARMACOLOGICAL REPOSITORY

Global traditional medical systems represent repositories of evolutionarily optimized chemical diversity. Asian medical traditions offer insights into mitochondrial energetics and longevity regulation, exemplified by concepts such as *Qi* (TCM) and Rasayana (Ayurveda). Mediterranean and Greco-Arab systems contribute cardiometabolic and anti-inflammatory scaffolds, while Amazonian and African traditions reveal sophisticated neuropharmacological synergies, including β-carboline–mediated monoamine oxidase inhibition and the neurocircuit-modulating effects of ibogaine.

By translating symbolic therapeutic constructs into molecular mechanismssuch as 5-HT_2A receptor agonism or synaptic plasticity modulationethnopharmacology emerges not as folklore conservation, but as a high-yield discovery platform for treatment-resistant and neurodegenerative disorders.

IV. ANALYTICAL PLATFORMS AND LEAD OPTIMIZATION

Modern extraction technologies, including supercritical fluid extraction (SFE) and ultrasound-assisted extraction (UAE), facilitate efficient recovery of thermolabile and low-abundance metabolites while minimizing solvent usage. To address rediscovery challenges, GNPS-based dereplication integrates LC–MS/MS molecular networking for rapid identification of known scaffolds and novel analogues. Reproducibility is further reinforced through dual standardization using chemical fingerprinting and DNA barcoding, ensuring taxonomic accuracy.

V. NETWORK PHARMACOLOGY AND POLY-TARGET MECHANISMS

Contemporary systems biology confirms that pharmacological synergy is quantifiable rather than anecdotal. Network pharmacology approaches reveal how secondary metabolites modulate pharmacokinetics, enhance bioavailability, and stabilize ligand–target interactions. Centrality analyses identify critical nodes within compound–protein

interaction networks, elucidating mechanistic convergence points.

VI. MECHANISTIC INSIGHTS

Inflammation and Cancer: Boswellic acids and curcuminoids attenuate NF-κBsignaling through inhibition of IKK activity, while alkaloids such as camptothecin and vincristine induce intrinsic apoptosis via mitochondrial membrane permeabilization. Polyphenolic compounds further suppress angiogenesis by modulating VEGFR-2–dependent PI3K/Akt/mTOR pathways.

Neurological and Metabolic Disorders

Ethnobotanical metabolites activate the autophagy–lysosome pathway, enhance incretin signaling, and function as AMPK-dependent caloric restriction mimetics, positioning them as systemic modulators rather than symptomatic interventions.

VII. FUTURE PERSPECTIVES: PRECISION ETHNOMEDICINE

The integration of omics technologies, artificial intelligence, and synthetic biology is shaping the emergence of Precision Ethnomedicine. Digital twins, microbial biosynthesis of scarce metabolites, and Ayurgenomics-guided patient stratification enable personalized deployment of multi-component formulations. This integrative framework transcends reductionism by restoring biological systems through evolutionarily informed, network-active interventions.

VIII. CONCLUSION

The modern resurgence of ethnopharmacology represents a decisive shift away from reductionist drug discovery toward a systems-oriented, evolutionarily grounded paradigm. By integrating indigenous medical knowledge with Reverse Pharmacology, network pharmacology, and advanced analytical technologies, ethnopharmacology reframes traditional remedies as pre-validated, high-value molecular blueprints rather than anecdotal artifacts.

The inefficiencies described by Eroom's Law reflect not only economic limitations but conceptual shortcomings inherent to single-target strategies. Ethnobotanical scaffolds demonstrate measurable poly-pharmacology, modulating convergent signaling hubs including NF-κB, AMPK, PI3K/Akt/mTOR, autophagy–lysosome pathways, and neuroplastic circuits. These properties validate traditional formulations as network-active therapeutics capable of addressing antimicrobial resistance, metabolic disorders, cancer, and neurodegeneration.

Equally important is the ethical dimension of translation. Compliance with the Nagoya Protocol, rigorous taxonomic authentication, and standardized phytochemical reporting are foundational to responsible advancement. The adoption of PRISMA–Ethnopharmacology, ConPhyMP guidelines, and clinical quality metrics ensures alignment with contemporary regulatory and pharmaceutical standards.

As omics, machine learning, and synthetic biology converge, ethnopharmacology is poised to lead the transition toward Precision Ethnomedicine. In this synthesis of ancestral wisdom and molecular precision, ethnopharmacology does not merely complement modern medicine—it offers a resilient, ethically grounded, and biologically coherent framework for future therapeutics.

REFERENCES

[1] Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 1981 to 2019. Journal of Natural Products, 83, 770–803.

[2] Patwardhan, B., Vaidya, A. D. B., & Chorghade, M. (2004). Reverse pharmacology and systems approaches for drug discovery and development. Current Science, 86, 789–799.

[3] Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. Nature Reviews Drug Discovery, 11, 191–200.

[4] Harvey, A. L., Edrada-Ebel, R., & Quinn, R. J. (2015). The re-emergence of natural products for drug discovery in the genomics era. Nature Reviews Drug Discovery, 14, 111–129.

[5] Atanasov, A. G., et al. (2021). Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology Advances, 39, 107372.

[6] Heinrich, M., et al. (2018). Best practice in ethnopharmacology—revised and expanded. Journal of Ethnopharmacology, 210, 1–7.

[7] Heinrich, M., et al. (2020). ConPhyMP—Consensus-based reporting guidelines for phytochemical characterization of medicinal plant extracts. Journal of Ethnopharmacology, 254, 112813.

[8] Hopkins, A. L. (2008). Network pharmacology: The next paradigm in drug discovery. Nature Chemical Biology, 4, 682–690.

[9] Corson, T. W., & Crews, C. M. (2007). Molecular understanding and modern application of traditional medicines: Triumphs and trials. Cell, 130, 769–774.

[10] WHO. (2014). Antimicrobial resistance: Global report on surveillance. World Health Organization.

[11] Cowan, M. M. (1999). Plant products as antimicrobial agents. Clinical Microbiology Reviews, 12, 564–582.

[12] Aggarwal, B. B., & Sung, B. (2009). Pharmacological basis for the role of curcumin in chronic diseases. Advances in Experimental Medicine and Biology, 595, 1–75.

[13] Fulda, S., &Debatin, K. M. (2006). Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. Oncogene, 25, 4798–4811.

[14] Ma, Q., et al. (2019). Caloric restriction mimetics: Towards a molecular definition. Nature Reviews Drug Discovery, 18, 531–548.

[15] Patwardhan, B., et al. (2015). Ayurgenomics: Integrating Ayurveda and genomics for stratified medicine. Journal of Ayurveda and Integrative Medicine, 6, 193–197.

[16] McEwen, B. S., & Akil, H. (2020). Revisiting the stress concept: Implications for affective disorders. Neuron, 107, 1033–1045.

[17] Wishart, D. S., et al. (2018). DrugBank 5.0: A major update to the DrugBank database. Nucleic Acids Research, 46, D1074–D1082.