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From Ethnobotany to Evidence: Integrative Strategies for Phytochemical Discovery and Therapeutic Translation

Dilshod Abdullayev[1], Soundarya Kasi[2], Nirmal Kumar[3], Sorabh Lakhanpal[4], Komal Patel[5], Danish Kundra[6], K. V. Navin Raja[7]

[1]Associate Professor, Department of Theory and Methodology of Physical Culture, Faculty of Physical Education and Sport, Jizzakh State Pedagogical University
[2]Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research, soundaryak@maher.ac.in
[3]Department of Pharmacology, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research, Enathur, Kanchipuram, Tamil Nadu 631552. nirmalkumar@maher.ac.in
[4]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab 144411, India. sorabh.lakhanpal@lpu.co.in
[5]Associate Professor, Department of Pharmacognosy, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India. komalnishit@gmail.com
[6]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, 140401, Punjab, India. danish.kundra.orp@chitkara.edu.in
[7]Assistant Professor, Department of Pharmacology, Vinayaka Missions Medical College, Karaikal, Vinayaka Mission's Research Foundation (DU), Tamil Nadu, India. kothengudidoctor@gmail.com

ABSTRACT: Ethnobotanical knowledge has been used to discover clinically useful natural products many times, but the conversion from traditional use to documented reproducibility of therapeutic benefit is inefficient. This review presents an integrative approach that links community-based knowledge to the botanical validation, contemporary extraction, chemical characterisation, bioactivity testing, multi-omics, network pharmacology, artificial intelligence, drug formulation and clinical validation. The suggested framework sees the discovery of phytochemicals not as a linear process looking to one single active ingredient, but as a process of generation evidence in an iterative manner. Specific attention is given to surveillance and documentation of plant species and their use, orthogonal analytical confirmation, mechanism-dependent screening, mechanism-based drug pharmacokinetics and mechanism-based toxicity characterisation, and early focus on product standardisation.

Computational approaches can be useful to speed up the annotation and prioritisation process, but the predictions of these approaches should be tested experimentally and reported openly. Other factors include fit-for-purpose formulations, well-designed clinical trials, pharmacovigilance, ethical access and benefit sharing, and sourcing sustainability. Combination of all these can lead to lesser false-positive discoveries, greater reproducibility and distinguish promising phytochemicals from insufficiently characterised extracts. Thus, a coordinated link from ethnobotany to evidence may be

beneficial for natural product drug discovery and for standardizing and evidence-based phytomedicines.

1. INTRODUCTION

Natural products have made significant contributions to contemporary pharmacotherapy, as medicines or as the models for the synthesis of semisynthetic and synthetic medicines. Experiments with approved drugs are still elucidating the long lasting effects of natural scaffolds, especially in oncology, anti-infective therapy, immunology and neurological disease (1,2). Ethnobotany enriches this chemical variation by specifying those plants having been used for specific symptoms, preparations and modes of application due to their cultural selection by the communities over the years. The data can be used to complement discovery libraries and increases the chances of identifying biologically relevant activity over random screening (3,4). Another example of the classic experiences suggests that the knowledge on medicinal plants can be used for new drug development if assessed from the point of view of modern pharmacology and chemistry (30). Traditional usage does not always translate into clinical effectiveness, however, and many of the promising observations remain obscure in the process. Many examples of traditional use do not convey information on the identity of the plants, the conditions of extraction, their chemical composition, the dosages used, the target organs and target organisms they act on and their safety profile. What's important, then, is not only to isolate more compounds, but to establish a chain of proof that shows a documented use can be replicated with an intervention and a clinically relevant response. Traditional research is fragmented with ethnobotanical, analytical chemistry, pharmacology, formulation, and clinical research done in separate projects. This fragmentation can lead to multiple redundancies, undermines reproducibility, and even enable promising computational or in vitro results to be published without sufficient exposure or safety data. The latter, on the other hand, is an integrative strategy that starts by aligning these disciplines, establishes progression rules based on the decisions and negative results, and guides plant selection and mechanistic hypotheses to improve. This review details such a route from ethnobotanical observation to therapeutic translation, highlighting focus on quality, experimental triangulation, computation, pharmacokinetics, formulation, clinical evidence, ethics, and sustainability.

2. ETHNOBOTANICAL KNOWLEDGE AS A FOUNDATION FOR PHYTOCHEMICAL DISCOVERY

Natural products have made significant contributions to modern pharmacotherapy as drugs and as models for semisynthetic and synthetic drugs. The long-lasting effects of the natural scaffolds, especially in oncology, anti-infective therapy, immunology and neurological disease, showed up again in the approved drug analyses that went on (1,2). Ethnobotany is a culturally-informed perspective on this chemical diversity whereby communities have been choosing plants for specific symptoms, preparations and routes of administration for a long time. This information can enhance the likelihood of finding bioactive compounds and enrich the discovery libraries relative to non-target screens. Examples from the traditional use of medicinal plants also demonstrate that knowledge of the plants may be relevant in contemporary drug discovery processes, provided it is approached with up-to-date methods in pharmacology and chemistry (30). But traditional use is not necessarily synonymous with clinical effectiveness and many promising observations are not translated well when taking into account issues relating to plant identity, extraction conditions, the chemical composition, dosage, engagement with the target, and the safety of the plants. The focus of the central challenge, therefore, is not just isolating increasingly more compounds, but establishing an irrefutable causal chain from a reported use to a repeatable intervention to a clinically relevant outcome. Traditional pipelines typically involve ethnobotanical surveys, analytical chemistry, pharmacology, formulation and clinical research as separate initiatives. This fragmentation helps to allow duplication, diminishes the strength of reproducibility, and allows for the development of findings that are attractive for computational or in vitro purposes without sufficient exposure or safety data. The integrative approach, by contrast, immediately establishes the link between these disciplines, establishes benchmarking decisions for advancement, and takes negative results to feed into plant selection and mechanistic hypotheses. Such a transition is described in this review from ethnobotanical observation to therapeutic translation, focusing on quality, experimental triangulation, mathematical aids, pharmacokinetics, formulation, clinical evidence, ethics and sustainability.

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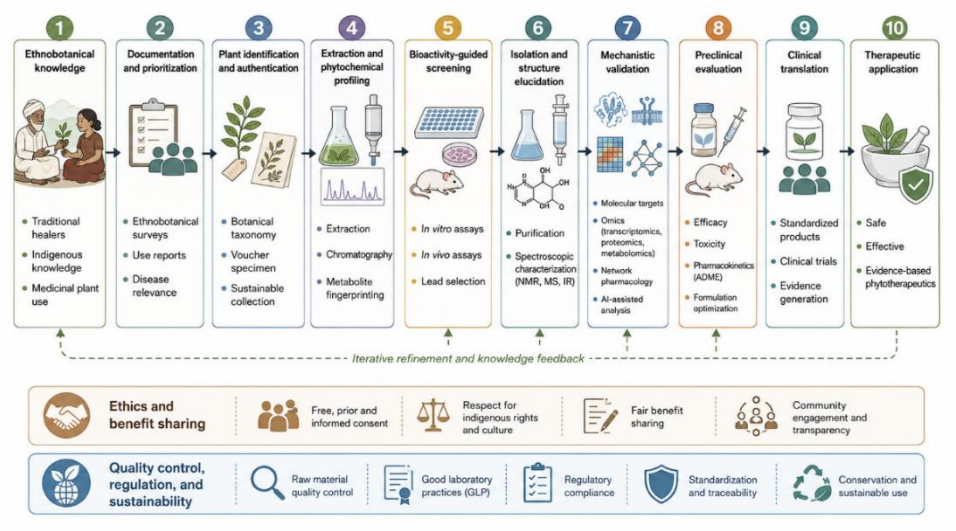

Figure 1: Ethnobotany-to-therapeutics translational pathway

3. PLANT AUTHENTICATION, COLLECTION, AND STANDARDISATION

All of the results obtained downstream are dependent on the identity and quality of the starting material. Authentication should include an expert taxonomy, voucher specimen deposited in a recognised herbarium, full collection data and, if necessary, microscopic, chromatographic or DNA based confirmation. Metabolite abundance can vary due to collection season, developmental stage, geography, soil, climate, process delay and storage time. GAPs are guidelines that can be used to implement traceability and contamination control practices and to ensure repeatable harvesting but must be tailored to each species and to the surrounding conditions of the wild harvest (7). Standardisation is more extensive than the measurement of one familiar compound. Macroscopic and microscopic identity, moisture, ash, limit of microorganisms, pesticides, heavy metals, mycotoxins, residual solvents, extractive values, chromatographic fingerprints, quantitative markers related to the activity, consistency of manufacture are possible specifications. The marker compounds can be active, analytical, or both, and should be selected for reasons of more than mere availability of a commercial standard (8). Orthogonal comparisons, reference extracts and retained samples produce a traceable material history on a batch to batch basis. This step is especially critical for clinical products, since an intervention that is not chemically and microbiologically reproducible cannot provide evidence of efficacy or safety that is interpretable.

4. EXTRACTION, ISOLATION, AND STRUCTURAL CHARACTERISATION OF PHYTOCHEMICALS

The extraction should be based on the research question, traditional preparation, the types of chemicals to look for, and the intended dosage form. Maceration, percolation, Soxhlet extraction, hydrodistillation and infusion are still useful and accessible extraction techniques that are scalable; ultrasound-assisted, microwave-assisted, pressurised-liquid, supercritical-fluid and enzyme-assisted extraction can minimise solvent usage and/or extraction time and can be more selective. Yield and composition can be influenced by the solvent polarity, solid to liquid ratio, particle size, temperature, time, pH, oxygen exposure, and light exposure; these should be recorded. If this results in a lower content of the active fraction, or co-extracts interfering constituents, a high extraction yield may not be desired. Drug design principles are applicable to natural product research, especially when combined with systematic biological and computational evaluation (15,16). The chemical profiling process can be supported with complementary platforms with increasing frequency. High performance liquid chromatography (HPLC) with ultraviolet or diode-array detection is used for routine fingerprinting and quantification, while LC-HRQTOFMS helps with comprehensive metabolite annotation (isotope patterns, accurate mass, fragmentation data). For volatile and derivatised compounds, gas chromatography-mass spectrometry is the preferred technique; in the case of nuclear magnetic resonance spectroscopy, the structures and stereochemical relationships of the compounds can be confidently established with relatively little dependence on reference standard. Rapid identity testing and process monitoring can be aided with the use of infrared and Raman spectroscopy. For more complicated extracts, the best evidence of identity is when the retention behaviour, exact mass, fragmentation, ultraviolet spectra, NMR and authentic standards all correspond (9). Derep can be used to avoid re-

isolation of known compounds and can be used to direct efforts towards new chemistry or new biological applications. Community spectral libraries and molecular networking can be used to cluster related ions and uncover analogue families and facilitate swift comparison between extracts (10). The molecular formula and candidate structures can be proposed by in silico tools like SIRIUS from tandem mass spectra, but these are just hypotheses until supported by orthogonal evidence (11). Therefore, the fractionation process should alternate chemical separation with testing for activity, and track the activity to go with one constituent or chemical family, or with interaction among the fractions in the process of bioassay. A summary of important extraction and analytical strategies and their practical considerations is presented in Table 1.

Table 1. Major extraction and analytical techniques used in phytochemical discovery.

Method	Primary output	Main strength	Key limitation
Infusion/decoction	Polar traditional extract	High ethnobotanical relevance; simple and scalable	Limited for non-polar compounds; heat may degrade labile constituents
Maceration/percolation	Broad solvent extract	Flexible and inexpensive	Long extraction time; high solvent use
Ultrasound-assisted extraction	Rapid enriched extract	Reduced time and solvent; moderate temperatures	Scale-up and cavitation conditions require optimisation
Supercritical-fluid extraction	Low-solvent lipophilic extract	Selective; minimal solvent residue	High equipment cost; less suitable for highly polar compounds
HPLC-DAD/UV	Fingerprint and quantification	Robust routine quality control	Limited structural information without standards
LC-HRMS/MS	Accurate mass and fragmentation profile	Broad coverage and rapid annotation	Isomers may remain unresolved; database-dependent
GC-MS	Volatile and derivatised metabolite profile	High chromatographic resolution and mature libraries	Requires volatility or derivatisation
NMR spectroscopy	Definitive structural and quantitative data	Non-destructive and highly reproducible	Lower sensitivity and greater sample requirement

5. BIOACTIVITY-GUIDED SCREENING AND PHARMACOLOGICAL VALIDATION

Bioactivity-guided discovery is most persuasive when the assay reflects the proposed therapeutic context and includes controls for common artefacts. Initial screening may use biochemical targets, cell-based phenotypes, organoids, microbial systems, or ex vivo tissues. Target-based assays are efficient and mechanistically focused, but they may miss permeability, metabolism, network effects, or multi-target activity. Phenotypic assays capture integrated responses, yet their readouts can be difficult to interpret. A staged strategy can use phenotypic screening for relevance, followed by target deconvolution and pathway analysis to explain the response. Extracts and phytochemicals can interfere with fluorescence, absorb light, aggregate proteins, chelate metals, alter pH, or cause non-specific membrane damage. These possibilities should be examined through orthogonal readouts, counterscreens, vehicle controls, concentration-response curves, cytotoxicity testing, and, when appropriate, time-of-addition experiments. Anti-infective claims are especially vulnerable to misleading results when inoculum, growth phase, solvent, endpoint, or host-cell toxicity are poorly controlled (12). Biological replication across independent extract batches is more informative than repeated wells from one preparation. Fractionation should not assume that the most active fraction contains the only relevant constituent. Synergy can improve potency or broaden pathway coverage, while antagonism can reduce toxicity

or activity; both are well documented challenges in natural-product research (13,14). Combination effects should be tested with appropriate models such as isobolograms, combination indices, response-surface analysis, or Bliss and Loewe frameworks rather than inferred from a single mixture. The desired output is a reproducible activity profile linked to defined chemistry, plausible target engagement, and an exposure range that can guide later pharmacokinetic and in vivo studies. This has been used for therapeutic purposes and has filtering for common artefacts. Biochemical markers, cell-based phenotypes, organoids, microbial systems or ex vivo tissues can be used for initial screening. Target-based assays are efficient and mechanistically specific, but may lack network effects, metabolism or multi-target activity. Phenotypic assays are measurements of integrated responses but may have ambiguous results. A staged approach may include phenotypic screening for relevance, target deconvolution and pathway analysis for explanation of the response. Extracts and phytochemicals may quench the fluorescence, absorb light, promote protein aggregation, chelate metals, change pH or non-specifically damage membranes. These possibilities should be explored using orthogonal readout, counterscreens, vehicle controls, concentration-response curves, cytotoxicity testing, and, if applicable, time-of-addition experiments. Inoculum, growth phase, end point, solvent, and host-cell toxicity are all important when assessing anti-infective activity, and a lack of control over any of these factors is likely to result in misleading conclusions (12). Various replicate extract batches are more informative than repeated wells from the same prepare. Fractionation cannot be based on the idea that the most active fraction is the only one of interest. Both synergism to increase potency or pathway coverage, and antagonism to decrease toxicity or activity are known issues in natural-product research (13,14) and can be addressed through synergy. Combination effects should be examined using suitable models, like isobolograms, combination indices, response surface analysis and Bliss and Loewe, and not be inferred from a single mixture. The aim of the work is to provide a reproducible activity profile, associated chemistry and likely targets, alongside an exposure window to help direct subsequent pharmacokinetic and in vivo studies.

6. INTEGRATION OF OMICS, BIOINFORMATICS, AND ARTIFICIAL INTELLIGENCE

While the ability to tie complex phytochemical mixtures to biological systems is a strength of the omics and computational techniques, the true power of the technologies lie in their prioritising and hypothesis generating capabilities. Untargeted metabolomics involves the study of chemical features of the metabolome between species, plant parts, seasons, extracts or active and inactive fractions. Discriminating features can be identified using multivariate analysis and related metabolite families, using tandem mass spectrometry and molecular networking. These data can be combined with data obtained from transcriptomics or proteomics or targeted measurements of pathways in treated cells or tissues to uncover convergent biological responses. This gives not only a list of molecules but a "map" that correlates the composition of the extract with the phenotypic changes observed. Particularly, network pharmacology is useful for multi-component preparations, which describe the relationship between compounds, predicted or measured targets, pathways, and disease module (17,18). Database is treated as proof, however, and this implies network diagrams are also potentially circular. The credibility of a network is determined by the compound identity, realistic exposure, confidence of target prediction, background selection and experimental confirmation. Overconnected proteins, in particular those widespread in all analyses, should not be prioritized as hubs because they do not necessarily have a special role. Better studies incorporate sensitivity analyses, different target-prediction methods, negative controls and binding assays, genetic perturbations or target-engagement techniques to validate selected edges. In the area of spectral annotation, machine learning can help identify what types of structures are likely to exhibit therapeutic or toxic properties, generate de novo compounds, and prioritize target/compound combinations. (19-21) Even when the assay is trained using publicly available data, it can include assay noise, chemical redundancy, publication bias and inadequate stereochemical coverage of natural products. When there are similar data points in both the training set and test set, random data splitting may overestimate the performance. Scaffold-aware or time-split validation, external test sets, uncertainty estimates, and applicability-domain analysis, therefore, are preferred. Methods that are explainable can uncover features that affect predictions, and can be used to ensure that medicinal chemists can distinguish meaningful structure-activity relationships from spurious correlations (20). The best way to work is to be iterative. Computational analysis ranks candidates and provides suggestions for possible mechanisms, experiments confirm identity, activity, engagement of target, and exposure, and the data are fed back into the model to enhance the ability to predict subsequent activity. This integration is represented in figure 2. A closed loop can decrease the number of samples advanced, emphasize informative negative results and maintain biological interpretability. Also, it promotes the use of transparent data structures, standard identifiers, open spectral deposition and reproducible code, all of which are vital for cross-laboratory validation.

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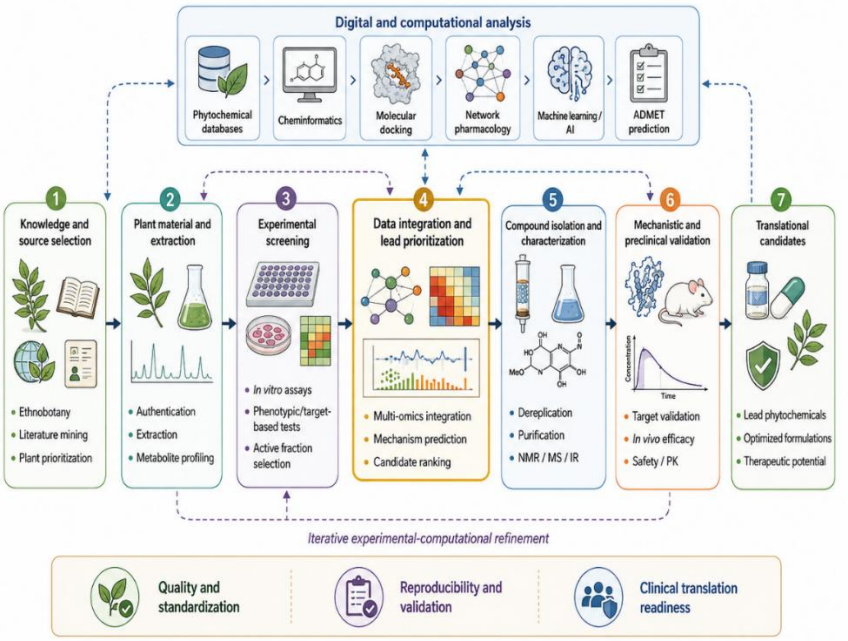

Figure 2: Integrated computational and experimental workflow for phytochemical discovery

7. PRECLINICAL EVALUATION OF SAFETY, EFFICACY, AND PHARMACOKINETICS

Preclinical progression should answer whether a defined phytochemical or standardised extract reaches the relevant tissue at a tolerated exposure and produces an effect consistent with its proposed mechanism. In vivo efficacy models should be selected for translational relevance rather than convenience, with prespecified endpoints, randomisation, blinding where feasible, and justified dose selection. Positive findings in one acute model are insufficient; replication in a complementary model or with an orthogonal biomarker improves confidence. Measuring drug or marker concentrations in plasma and target tissue is essential because an apparent pharmacodynamic effect without plausible exposure may reflect stress, toxicity, or an unrelated mechanism. Absorption, distribution, metabolism, and excretion studies identify solubility limits, permeability, protein binding, metabolic pathways, active metabolites, transporter effects, and clearance. Extract studies require additional attention to constituent-constituent interactions and whether the measured marker represents the broader active material. Toxicology should move from basic cytotoxicity and acute tolerability to repeat-dose studies, clinical chemistry, histopathology, genotoxicity, safety pharmacology, and, where relevant, reproductive or developmental risk. Particular attention is needed for reactive metabolites, cardiac ion channels, liver injury, immunotoxicity, and interactions with drug-metabolising enzymes. Attrition in drug development frequently arises from insufficient efficacy, safety, or pharmacokinetic properties (22,23). Integrating these measurements early helps avoid advancing a compound because of potency alone. A lead should therefore be judged by a balanced profile: chemical tractability, reproducible activity, selectivity, mechanism, exposure, safety margin, scalable supply, and suitability for formulation.

8. FORMULATION AND DRUG-DELIVERY STRATEGIES FOR PHYTOCHEMICALS

Failing to find a match on the physicochemical properties of many phytochemicals to the proposed route is the reason behind many failing to translate. Metabolism and efflux are important determinants that can give a very different picture of the in vitro potency compared to the exposure achieved in humans, due to low solubility in the aqueous phase, chemical instability and extensive first-pass clearance. The compound, curcumin, is a well-established case in which great biological interest is limited by its biological/compatibility-insensitive bioavailability and formulation issues (24). Once the target product profile (TPP) has been defined (including route, dose, site of action, release pattern, patient population, storage conditions and acceptable excipients), formulation development should start. The use of conventional methods like salt formation, co-solvents, cyclodextrin inclusion, solid dispersions, phospholipid complexes or self-emulsifying systems can be adequate. Apparent solubility enhancements, protection of labile molecules, changes in distribution, and local and controlled delivery are possible advantages of using nanoparticles, liposomes, nanoemulsions, polymeric micelles, lipid carriers, and hydrogels (25). But with

higher complexity in formulation, there can be scale-up, sterilisation, stability, reproducibility, and regulatory challenges. Comparative studies should, therefore, demonstrate improvement in a clinically relevant property of the delivery system, not just a change in particle size. By linking formulation performance to exposure and response a pharmacokinetics-pharmacodynamic (PKPD) modelling approach can be used to link the performance of these formulations to their effects. The chosen product should have identity, potency, impurities, dissolution/release profile, physical stability and microbial quality charactarization, as well as packaging compatibility. Some of the representative phytochemicals demonstrating successful translation and ongoing formulation or evidence gaps are given in Table 2.

Table 2. Representative phytochemicals illustrating successful and incomplete therapeutic translation.

Phytochemical and source	Major mechanism	Therapeutic status	Translational lesson
Paclitaxel - Taxus spp.	Stabilises microtubules and blocks mitosis	Approved anticancer medicine	Landmark natural-product drug; supply improved through semisynthesis and cultivation
Artemisinin - Artemisia annua	Heme-activated reactive intermediates damage parasite proteins	Artemisinin derivatives are standard antimalarial agents	Successful translation required combination therapy and resistance stewardship
Vincristine - Catharanthus roseus	Inhibits microtubule assembly	Approved antineoplastic medicine	Potent but dose-limited by neurotoxicity; complex supply chain
Galantamine - Galanthus spp.	Acetylcholinesterase inhibition and nicotinic receptor modulation	Approved for symptomatic treatment of Alzheimer disease	Demonstrates value of ethnobotanical and pharmacological convergence
Cannabidiol - Cannabis sativa	Multi-target modulation of neuronal excitability	Purified formulations approved for selected seizure syndromes	Product purity, dose, interactions, and regulatory status are critical
Curcumin - Curcuma longa	Pleiotropic modulation of inflammatory and redox pathways	Extensively studied; no broad drug approval	Translation limited by bioavailability, formulation heterogeneity, and variable trial quality

9. CLINICAL TRANSLATION AND EVIDENCE-BASED EVALUATION

Evaluation of phytochemicals and standardised extracts for clinical use must be as rigorous as any other therapeutic intervention, taking into account the added complexity of product identity. The investigational material should be produced in an appropriate quality system and be chemically characterised, stable for the length of the trial, and be traceable by batch. Traditional exposure, preclinical safety, pharmacokinetics and concentration needed for target engagement should be factored into dosing decisions. Small studies determine tolerability, exposure, food effects and biomarkers prior to attempting large efficacy studies. RCTs should have clinically relevant eligibility criteria, comparator groups, adequate power, intention to treat analysis, blinding (when possible), and prespecified outcomes. Reporting of herbal intervention also includes botanical name, part of the plant which can be changed, extraction ratio, solvent, drug-extraction ratio, marquer content, excipients, dose, treatment regimen and quality testing. The CONSORT reporting guideline for herbal interventions is elaborated, and is useful for reporting (26). While biomarkers can aid in mechanism and dose selection, they should not be used in lieu of patient important outcomes, unless proven as a surrogate. However, it is important that herb-drug interactions be evaluated proactively, since phytochemicals could interact with enzymes, transporters, coagulation, blood pressure, glucose, or the central nervous system (27). Concomitant medications, medication adherence, adverse events, laboratory abnormalities, and reasons for

withdrawal should be collected during trials. Pre-market or post-market usage is equally essential as rare liver injury, allergy, contamination, substitution, and interactions may not be expressed in small trial (28). Comparability of the products is an important factor to be taken into account when considering evidence synthesis. Pooling evidence from studies of chemically different extracts under the same plant name can lead to a misleading estimate. If the clinical product is of the same material or an evolution of this material that was used for the analytical and preclinical studies, then the translation will be strong. Common barriers to translation are associated with practical enabling strategies as depicted in figure 3.

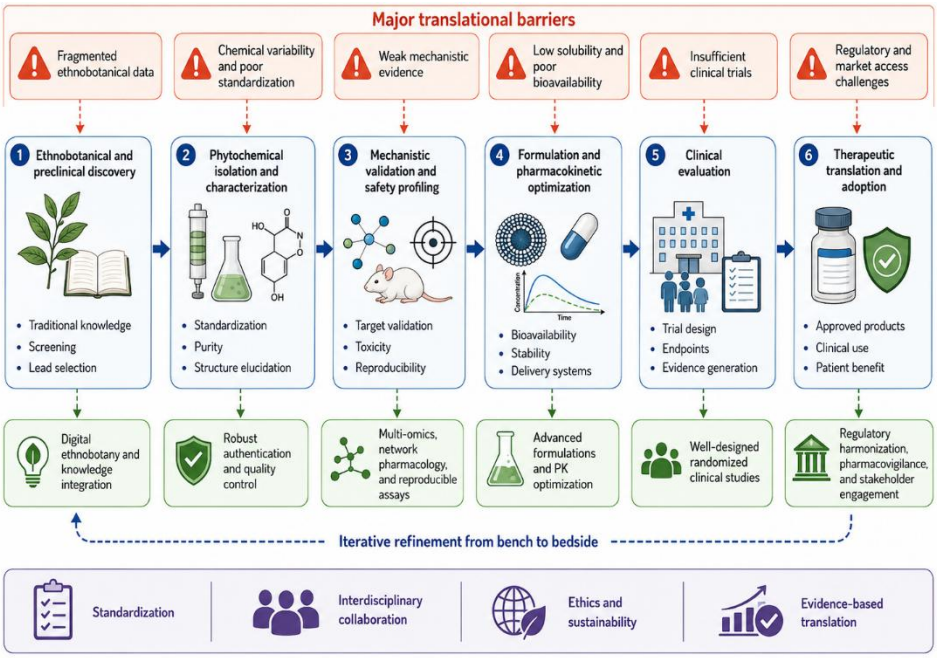

Figure 3: Translational barriers and enabling strategies from laboratory discovery to clinical application.

10. REGULATORY, ETHICAL, AND SUSTAINABILITY CONSIDERATIONS

The definitions of these regulatory categories differ among jurisdictions, by intended uses, ingredients, past uses, and degree of processing. This product could be a medicine, a traditional herbal medicinal product, a botanical drug, a dietary supplement, or a cosmetic, and each of these has distinct quality, evidence, labeling and pharmacovigilance requirements. Initial contact with the regulators can help determine if the desired development is a registered active ingredient, a standardised multi-component extract, or a traditional product based on the results of a bibliographic search. Consistency, stability, and truthful claims are key points common to both pathways and identity and contamination control, even if both are not required for each pathway. In the case of an ethical translation, it starts before the sample is collected. Indigenous or local knowledge must not be used without respect for customary governance; without recognising the knowledge holders; and without giving them a fair share in the benefits. The Nagoya Protocol establishes an international convention for access to genetic resources and fair and equitable sharing of benefits from their utilisation (29). The benefit is not limited to payment in one sum, but can involve co-authorship (if appropriate), training, infrastructure, community health initiatives, licensing revenue, shared intellectual property or anything else. Sustainability is also an expectation of science. A range of destructive harvesting practices, reliance upon slow growing wild species and commercial demand can compromise the quality of biodiversity and long-term supply. Cultivation, tissue culture, synthetic biology, use of renewable parts of plants and conservation partnerships should all be taken into account when selecting a lead, rather than at the end of the efficacy stage. The source for a potential therapeutic phytochemical cannot be legally, ethically and readily obtained at scale, then it cannot be considered to be truly translatable.

11. CURRENT CHALLENGES AND RESEARCH GAPS

There are still frequent issues with the field with respect to reproducibility, comparability, and causal interpretation. The names of plants might be incorrect or the species could be confused, or voucher specimens are not present and chemical profiles are limited to 1 or 2 markers, or the extraction method may not have been fully described. Concentrations of activity in vitro are

very rarely therapeutic concentrations in vivo and toxicity, solubility and assay interference are not tested. Computational studies can produce large compound-target networks, and even if the compounds are present, absorbed and able to reach the target, it is not necessarily the case. On the other hand, the reductionist isolation can overlook beneficial matrix effects or complementary constituents. Small sample sizes, fragmented products, brief follow-up period, several outcomes and underreporting of adverse events affect the clinical evidence. Weak leads receive repeated investments because the negative or inconclusive results are not seen. Several of these issues might be addressed with shared reference extracts, open spectral data, standard reporting checklists, preregistered protocols, and independent replication. More cooperation among communities, taxonomists, pharmacognosists, analytical chemists, computational scientists, pharmacologists, formulation experts, clinicians and regulators is necessary so that information generated at each step can be applied by the following steps.

12. FUTURE PERSPECTIVES

Discovery of the phytochemicals in the future will likely be more data intensive, mechanistic and more patient-based. Documentation and traceability could be enhanced with portable spectroscopy, geospatial tools, digital herbaria and community-governed databases with the important caveat of protecting sensitive TK. Single-cell and spatial omics may identify the cell populations responding to complex extracts and organoids and organ-on-chip may deliver more human-relevant models of efficacy, metabolism and toxicity. Tracing with stable isotopes and sophisticated imaging can provide understanding of the fate of parent compounds and metabolites in tissues. Artificial intelligence has the potential to aid in plant selection, metabolite prediction, formulation optimization, and prioritization of patients potentially most likely to benefit, but these efforts will be limited by the availability of a representative data set, transparency of uncertainty, and prospective validation. The use of adaptive clinical and pharmacometric designs can optimize dose selection and minimize exposure of participants to sub-optimal doses. The identity of the product must be preserved when real world data are used to complement trials to describe longitudinal safety and usage patterns. The most critical change will be cultural: from positive findings to building up evidence, pooling evidence across multiple studies, and making evidence mergeable. Discovery programmes that set criteria for progression, archive negative data and include parallel programmes for quality, mechanism, exposure, safety, clinical relevance, ethics, and supply will be more likely to deliver innovative and credible therapies.

13. CONCLUSION

While ethnobotany can be an excellent starting point for phytochemical discovery, the translation of ethnobotanical use to a therapeutic application goes beyond mere historical use or in vitro activity. The best pathway involves plant authentication, reproducible extraction, detailed chemical characterization, mechanism-driven screening, computational prioritisation, in-depth pharmacokinetics, careful toxicology assessment, drug formulation, thorough clinical testing, and proper governance. Use of iteration between experimental and computational evidence can help eliminate false positives early on and ensure clinically meaningful questions remain. Similarly, ethical benefit sharing and sustainable sourcing safeguards communities and biodiversity to enable the detection of discovery. Quality, efficacy, safety, exposure, and implementation are interlinked issues; and it is possible to shift the ball from descriptive ethnobotany to standardised phytomedicines or natural-product leads, with a clear chain of evidence, in the context of these issues.

Declarations

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