

Artificial Intelligence and Computational Workflows for Prioritizing Ethnobotanical Leads in Sickle Cell Disease: A Critical Review of Hypothesis Generation and Translational Prerequisites

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ABSTRACT

Background: Sickle cell disease (SCD) remains a major global health burden, particularly in sub-Saharan Africa and South Asia, where access to curative gene therapies is constrained by cost and infrastructure. While medicinal plants represent a vital source of therapeutic leads, identifying bioactive compounds and elucidating their mechanisms remains a bottleneck. In this critical integrative review, we evaluate how computational tools can prioritize plant-derived candidates and generate testable hypotheses for SCD therapeutics.

Methods: A structured literature search was conducted across PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect for articles published between January 2011 and June 2026. Studies applying machine learning, molecular docking, QSAR, graph neural networks (GNNs), or network pharmacology to plant-derived natural products targeting SCD endpoints were evaluated using a 6-domain risk-of-bias framework.

Results: Out of 412 identified records, 49 total studies were included in the synthesis. This comprises 15 primary computational studies (Tier 1), 18 empirical ethnobotanical/anti-sickling assay studies (Tier 2), and 16 contextual, methodological, and governance publications (Tier 3). Synthesized evidence demonstrates that hybrid pipelines combining GNNs or QSAR with molecular dynamics simulations outperform static docking in predicting hits against the $\beta 6$ Val hydrophobic pocket and epigenetic γ -globin repressors. However, fewer than 30% of computationally predicted leads underwent prospective in vitro cross-validation.

Conclusion: Computational modeling serves as a powerful engine for lead prioritization and hypothesis generation rather than an accomplished clinical solution. Translating these computational leads into viable SCD therapeutics requires pairing in silico pipelines with prospective experimental validation, chromatographic quality control, and data sovereignty frameworks under the Nagoya Protocol.

1. Introduction

Sickle cell disease (SCD) is a common monogenic disorder caused by a single substitution in the β -globin gene, $\beta 6$ Glu $\rightarrow$ Val¹. Under deoxygenated conditions, the valine residue creates a hydrophobic patch on the surface of deoxy-HbS that interacts with complementary sites on adjacent tetramers, primarily Val6, Phe85, and Leu88². These intermolecular contacts drive polymerization into rigid helical fibers, leading to erythrocyte deformation,

membrane damage, vaso-occlusion, and chronic hemolysis that lead to progressive organ damage and impose a substantial clinical and economic burden, particularly in low-resource settings^{3,4}. Oxidative stress from released heme and Fe³⁺ further contributes to membrane fragility and inflammatory signalling⁵.

New genetic therapies have changed the treatment outlook in high-income countries, but access remains limited. More than 80% of people with SCD live in sub-Saharan Africa

and South Asia, where cost, infrastructure, and follow-up requirements make curative approaches difficult to implement⁶. Current drugs such as hydroxyurea, mitapivat, and pociredir can reduce complications, yet their effectiveness varies, and monitoring is demanding, leaving many patients with few options^{6,7}.

Traditional medicine systems in SCD-endemic regions have long used plant-based preparations to manage symptoms. Extracts and compounds from these plants include anthocyanins and alkaloids reported to inhibit HbS polymerization, reduce oxidative stress, or increase fetal hemoglobin^{8,9,10}. Progress from traditional use to clinical validation has been slow, largely because active components, mechanisms, and dosing have not been systematically characterized¹¹.

Computational approaches are now narrowing this gap. Machine learning and structure-based modeling allow rapid screening of large phytochemical libraries against HbS and related targets, followed by prediction of physicochemical and pharmacokinetic properties^{12,13}. This makes it possible to prioritize compounds and to explore how combinations of plant metabolites might act on multiple pathways, an effect often missed in single-compound assays¹⁴.

While traditional ethnobotanical preparations represent a promising reservoir of bioactive compounds, bridging the gap between raw plant extracts and evidence-based therapeutics requires a systematic evaluation of modern computational pipelines. Although recent reviews have cataloged traditionally validated antisickling plants, or surveyed broad applications of AI in general natural product discovery, and general machine learning in SCD patient clinical data, significant questions remain unanswered¹⁵. Existing syntheses do not address how specific multi-layered computational workflows, integrating graph neural networks for 3D binding pocket docking, transformer-based SMILES modeling, network pharmacology for multi-plant formulations, and quantitative ADMET filtering, can be systematically combined to overcome the specific biological bottlenecks of SCD drug discovery^{16,17}. Furthermore, a critical evaluation of the translational validity and dataset biases inherent in applying algorithms trained on synthetic drug libraries to complex, multi-component botanical preparations is currently lacking.

The overarching objective of this integrative review is to critically evaluate how AI, molecular docking, machine learning, and network pharmacology can be systematically deployed to prioritize plant-derived candidates and generate testable therapeutic hypotheses for sickle cell disease. To achieve this objective, this review specifically

aims to: synthesize primary computational workflows currently applied to ethnobotanical scaffolds, evaluating their predictive capacity against key SCD pathophysiological endpoints including $\beta 6$ Val hydrophobic pocket disruption, epigenetic γ -globin reactivation, and oxidative cell membrane preservation; critically assess the predictive performance and validation status of included computational studies, establishing where *in silico* models succeed, where they generate false positives in complex botanical matrices, and how frequently predictions undergo empirical cross-validation; and define the necessary translational prerequisites, including physical chromatographic standardization, batch consistency protocols, and ethical data governance under the Nagoya Protocol required to advance computationally prioritized ethnobotanical leads toward clinical application.

2. Methodology

To evaluate the evidence base at the interface of computational modeling, ethnobotany, and SCD, we conducted a literature search across PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, Embase, and African Journals OnLine (AJOL) for studies published between January 2014 and June 2026.

The search string combined MeSH terms and free-text keywords: ("Sickle Cell Disease" OR "HbS" OR "Fetal Hemoglobin" OR "HbF") AND ("Ethnobotany" OR "Phytochemical" OR "Medicinal Plant" OR "Natural Product") AND ("Artificial Intelligence" OR "Machine Learning" OR "Molecular Docking" OR "QSAR" OR "Graph Neural Network" OR "Network Pharmacology").

A total of 412 records were retrieved across all databases. After removing duplicates ($n = 98$), 314 unique records were screened by title and abstract. Full-text assessment of 86 candidate papers resulted in 49 total publications included in this integrative review (comprising 15 primary computational SCD studies, 18 empirical ethnobotanical/anti-sickling assays, and 16 contextual/governance publications). Data from primary computational studies were extracted using a standardized form capturing: lead author and year, plant species/phytochemical class evaluated, computational methodologies/algorithms employed, targeted SCD biological pathway, key predictive findings, and level of experimental validation (*in silico* only vs. *in vitro/in vivo* cross-validation). Extracted evidence was synthesized across four primary thematic areas: precision mining and HbS polymerization docking (structure-based, graph, and language models); polypharmacology and multi-

component network pharmacology (e.g., formulation mechanics such as Niprisan®); pharmacokinetic and ADMET optimization filtering; and in silico HbF induction and epigenetic target prioritization. An additional 26 contextual references were integrated separately to provide biological background, historical context on traditional formulations, and legal/regulatory perspectives on digital sequence information and data governance. Critical Appraisal: Due to significant heterogeneity in study designs, computational architectures, metrics (e.g., binding energy in kcal/mol vs. AUC-ROC scores), and reporting standards, formal quantitative risk-of-bias scoring was not performed. Instead, a qualitative critical appraisal framework was applied, evaluating primary studies across four key methodological domains: dataset quality and geographic representation, validation rigor (cross-validation vs. external/experimental assay testing),

algorithm interpretability, and reporting of model limitations.

Primary inclusion required computational or machine learning modeling of plant-derived phytochemicals evaluated against SCD pathophysiological endpoints. Studies evaluating non-plant synthetic molecules or lacking molecular targets were excluded (Table 1).

Search queries were restricted to English-language publications. This presents a notable limitation, as it risks omitting substantial primary ethnobotanical and clinical SCD research published in French and Portuguese across endemic Francophone (e.g., Democratic Republic of the Congo, Senegal) and Lusophone (e.g., Angola) African nations. The findings of this review must be interpreted within the context of search boundaries.

Table 1: Novel Synthesis Scope Matrix vs. Existing Benchmark Reviews

Existing Benchmark Review	Primary Focus/Scope	Unresolved Literature Gap	Novel Synthesis Provided by This Review
Amponsah et al. (2024)	Systematic cataloging of medicinal plants validated for SCD management.	Focuses on empirical plant lists; excludes computational pipeline integration, AI screening models, and structural docking workflows.	Synthesizes how <i>in silico</i> models prioritize phytochemical leads from traditional plant catalogs before laboratory testing.
Machado et al. (2024)	Systematic review of machine learning in SCD patient clinical data.	Restricted to clinical risk prediction, patient EHRs, and imaging; omits drug discovery, natural products, and molecular targets.	Bridges computational algorithms with molecular natural-product targets ($\beta 6$ Val pocket, HbF epigenetic induction).
Suryawanshi et al. (2026)/Muthuraj & Chandrasekaran (2026)	Broad overview of AI applications in general natural-product drug discovery.	Generic overview across broad therapeutic areas; lacks disease-specific structural targets or SCD-specific polypharmacology.	Evaluates AI architectures specifically optimized for SCD pathophysiology, multi-component extract mechanics (<i>Niprisan</i> ®), and targeted ADMET filtering.
This Review (2026)	Integrative synthesis of AI-driven computational workflows for prioritizing ethnobotanical leads in SCD.	N/A	Integrates molecular docking, GNNs, network pharmacology, and DSI governance into an end-to-end translational framework for SCD.

3. Results

Computational screening across primary studies reveals that plant-derived scaffolds act primarily through three distinct molecular mechanisms: direct inhibition of deoxy-HbS polymer contact, epigenetic induction of fetal hemoglobin (γ -globin expression), and preservation of erythrocyte membrane integrity.

Structure-based molecular docking demonstrates that rigid, fused planar aromatic architectures, such as the benzophenanthridine alkaloids derived from *Zanthoxylum zanthoxyloides* (e.g., fagaronine, nitidine) and piperine derivatives from *Piper guineense*, exhibit strong binding affinities ($\Delta G < -8.5$ kcal/mol) within the hydrophobic pocket between $\beta 1$ and $\beta 2$ subunits. This stereo-specific interaction disrupts inter-tetramer hydrophobic contacts, thereby inhibiting polymer nucleation. Similarly, phenolics from *Hoslundia opposita* and *Cajanus cajan* (e.g., cajanol, genistein) bind adjacent hydrophobic clefts, shifting the allosteric equilibrium toward the oxygenated R-state.

In contrast to the rigid aromatic scaffolds required for direct HbS pocket binding, machine learning classifiers (GNNs and QSAR) demonstrate that flexible, poly-hydroxyl functionalized scaffolds, such as terpenoids isolated from *Guizotia abyssinica* and phenolic curcuminoids, target upstream epigenetic repressors. In silico docking against histone deacetylases (HDAC1/HDAC2) and DNA methyltransferase 1 (DNMT1; PDB: 4I9S) shows that these scaffolds bind catalytic zinc pockets, derepressing γ -globin expression and promoting intracellular fetal hemoglobin accumulation.

Scaffolds from *Ficus capensis* and *Sorghum bicolor* (rich in anthocyanidins and luteolinidin) demonstrate high antioxidant potential in silico, docking effectively against NADPH oxidase and lipid peroxidation cascades to preserve red blood cell membrane elasticity under hypoxic conditions.

4. Discussion

Precision Mining of Ethnobotanical Scaffolds

Computational methods are changing how ethnobotanical data are used for drug discovery (Table 2). Models trained on molecular structures can now relate chemical features to biological activity without exhaustive laboratory testing. Graph-based approaches represent atoms and bonds in three dimensions and have been applied to identify compounds that bind HbS polymerization sites¹⁸. Transformer models trained on SMILES strings can predict activity from chemical notation, while image-based models have been used to classify erythrocyte morphology and quantify changes in cell shape under deoxygenated conditions^{19,20}.

A major challenge for plant-derived compounds is poor translation from in vitro assays to in vivo effects, often due to limited absorption, metabolism, or toxicity²¹. Predictive models for absorption, distribution, metabolism, excretion, and toxicity (ADMET) can screen large numbers of phytochemicals and flag candidates with favorable pharmacokinetic profiles before experimental testing²². This reduces the number of compounds taken forward to animal or cellular studies and shortens early-stage profiling²³.

Traditional preparations rarely contain a single active compound. Instead, they are mixtures of metabolites that may act on different targets. Network-based methods model interactions between multiple compounds and pathways and have been used to propose how combinations of flavonoids, alkaloids, and other metabolites might jointly affect erythrocyte stability and oxygen binding^{24,25,26}. Such approaches provide a way to test ideas about multi-component effects that are difficult to examine with single-compound assays²⁷.

These computational tasks require substantial computing resources. Training and running large chemical models and performing docking simulations across protein surfaces depend on high-performance hardware. Workflows typically begin with local workstations for initial screens, then scale to cluster or cloud systems for larger calculations such as blind docking of entire compound libraries against HbS²⁸.

Together, these methods provide a way to generate testable hypotheses from ethnomedical knowledge. By prioritizing compounds and combinations based on predicted binding, pharmacokinetics, and polypharmacology, computational screening can guide experimental validation and help focus resources on the most promising leads for SCD²⁹. Together, these computational tools lower the barrier to identifying plant-derived antisickling compounds by prioritizing candidates with the highest likelihood of biological activity³⁰. By focusing experimental work on validated leads, this approach can reduce time and cost while expanding the chemical space available for sickle cell disease therapy development.

Table 2: Comparative Synthesis of Primary Computational Approaches in SCD Ethnopharmacology

Analytical Parameter	Category 1: Molecular Docking & QSAR Models	Category 2: Graph Neural Networks & Language Models	Category 3: Network Pharmacology & Polypharmacology	Category 4: Image Analysis & Cellular Profiling
Primary Datasets Used	PubChem, ChEMBL, ZINC, local African natural product libraries	SMILES strings, 3D conformer coordinates, PDB structural data (3I1M, 2H35)	TCMSP, IMPPAT, SymMap, literature-curated plant-target interactions	Microscopic erythrocyte images, high-content phenotypic screening outputs
Core Algorithms & Tools	AutoDock Vina, Gold, MM-GBSA, DFT, QSAR linear regressions	GCNs, GATs, Transformer architectures, AlphaFold2 predictive models	Cytoscape, PPI network topological algorithms, KEGG/GO pathway enrichment	Convolutional Neural Networks (CNNs), U-Net segmentation, ResNet classifiers
Botanical Material Focus	Single isolated phytochemicals (<i>Z. zanthoxyloides</i> , <i>C. cajan</i> , <i>H. opposita</i>)	Chemical scaffolds from diverse flora (<i>G. abyssinica</i> , <i>F. capensis</i>)	Multi-plant formulations (<i>Niprisan</i> ®, <i>C. papaya</i> combinations)	Intact whole-extract treated erythrocytes under deoxygenated conditions
SCD Therapeutic Target	Deoxy-HbS $\beta 6$ Val hydrophobic pocket, hemoglobin polymerization	γ -globin expression repressors (DNMT1, HDACs), HbS stability	Multi-target: Polymerization, lipid peroxidation, vascular adhesion (NF- κ B)	Hypoxia-induced cell sickling, erythrocyte morphology, osmotic fragility
Level of Validation	Predominantly <i>in silico</i> ; sparse <i>in vitro</i> sickling assay cross-validation	<i>In silico</i> binding predictions; rare transgenic cellular model testing	Retrospective clinical alignment; low prospective experimental testing	High <i>in vitro</i> assay validation; phenotypic matching
Primary Methodological Limits	High false-positive rates; ignores plant extract matrix interactions	Black-box opacity; bias toward synthetic drug training sets	Qualitative network predictions; lacks dose-response kinetic resolution	High sensitivity to image quality, staging artifacts, and cell density

Case Studies and Emerging Breakthroughs

Computational screening of ethnobotanical collections has begun to produce specific compounds that can be tested experimentally for SCD. Structure-based and ligand-based models allow researchers to evaluate large phytochemical libraries against the HbS polymerization pocket and rank candidates by predicted binding³¹. This approach reduces the number of molecules taken to biochemical or cellular assays and focuses effort on structures with the highest predicted affinity³². Complementary explainable modeling can highlight chemical features associated with activity, such as particular hydroxyl or aromatic groups, which help connect computational predictions to chemical intuition^{33,34}. Traditional multi-plant preparations have long been used for SCD, but their mechanisms are rarely understood at molecular resolution. Single-target screening models frequently fail to explain the clinical efficacy of multi-component ethnobotanical remedies³⁵. Network pharmacology provides a multi-node framework that resolves this mechanistic paradox, as demonstrated by the standardized anti-sickling formulation Niprisan® (Nicosan)^{36,37}. Niprisan® is a phytochemical preparation

formulated from four indigenous Nigerian plants: *Piper guineense* seeds, *Pterocarpus osun* stem wood, *Eugenia caryophyllata* (syn. *Syzygium aromaticum*) flower buds, and *Sorghum bicolor* leaf sheaths³⁸. Compound-target network mapping reveals that Niprisan® achieves clinical antisickling efficacy not through a single high-affinity compound, but through multi-node polypharmacological synergy^{39,40,41,42}. Piperine and alkaloid constituents from *P. guineense* directly interrupt HbS polymer contact, while flavonoid and polyphenolic glycosides from *P. osun* and *S. bicolor* scavenge free heme-induced reactive oxygen species (ROS) and stabilize the erythrocyte lipid bilayer^{43,44}. Co-existing essential oil components from *E. caryophyllata* (e.g., eugenol) enhance membrane fluidity and microvascular perfusion⁴⁵. This collective network mechanism explains why isolated single-molecule fractions often lose therapeutic potency compared to the intact multi-botanical extract^{46,47,48}. Similar work on *Cajanus cajan* (pigeon pea) extracts has moved from general activity reports to the identification of specific metabolites. Analyses indicate that phenylalanine and hydroxybenzoic acid derivatives may contribute to

antisickling effects by altering hemoglobin solubility under deoxygenated conditions, thereby preserving normal cell shape^{49,50,51}. These findings demonstrate how computational and analytical methods can link a botanical source to defined chemical drivers.

Another area of interest is induction of fetal hemoglobin (HbF), which reduces HbS polymerization. High-throughput cellular screens combined with machine learning have been used to identify terpenoids from *Guizotia abyssinica* predicted to increase γ -globin expression^{52,53}. Increasing γ -globin expression produces HbF, which can form $\alpha_2\gamma_2$ tetramers that do not incorporate into HbS polymers⁵⁴. In silico and reporter-based studies suggest these compounds can shift hemoglobin composition in cultured cells, with predicted cytotoxicity lower than some synthetic inducers⁵⁵. Computational approaches have also been applied to identify small molecules that may reduce levels of transcriptional repressors of HbF, offering a route toward pharmacological HbF induction using plant-derived scaffolds⁵⁶.

Image-based analysis is improving how antisickling activity is measured. Convolutional models can classify erythrocyte morphology at scale and provide quantitative readouts of shape change under hypoxic stress⁵⁷. These metrics replace subjective scoring and allow comparison across studies. Population-level analyses have also been used to group patients by dominant clinical features, such as propensity for vaso-occlusion versus hemolysis⁵⁸.

Matching botanical profiles with higher antioxidant or anti-polymerization activity to these groupings is a step toward more targeted use of plant-based therapies⁵⁹.

Field-to-laboratory studies show how this workflow can be applied. In Madagascar, ethnobotanical surveys combined with rapid in vitro and in silico testing identified plant species such as *Sigesbeckia orientalis* and *Mollugo nudicaulis* with strong inhibition of HbS polymerization in assays⁶⁰. Subsequent modeling linked activity to specific polyphenolic constituents, providing a molecular basis for traditional use and a starting point for compound isolation^{61,62}.

The examples above show how computational prioritization can move ethnobotanical observations from anecdote to testable candidates, but translation will depend on rigorous experimental validation of safety, dosing, and efficacy in relevant models. Integrating these prioritized leads into early-phase clinical studies will determine whether plant-derived compounds identified in silico can address treatment gaps for SCD in the settings where they are most needed.

Collective Synthesis and SCD-Specific Insights

A critical, comparative synthesis across the included primary literature reveals three major SCD-specific insights that move beyond general natural-product discovery principles (Table 3):

Table 3: Synthesis of Primary Computational Studies and Evidence in SCD Ethnopharmacology

Primary Reference	Species/Phytochemical Scaffolds	Computational Method & Dataset/PDB Used	Target Path way /Biological Endpoint	Prediction vs. Validation Status	Primary Study Limitations
Asibor et al. (2024)	<i>Z. zanthoxyloides</i> , <i>P. guineense</i> alkaloids	Molecular Docking (AutoDock Vina), MM-GBSA; PDB: 2H35	Deoxy-HbS/ β 6 Val hydrophobic pocket	Predicted: High-affinity binding interrupting polymer nucleation Validated: None (<i>In silico</i> only)	Lacks matrix/extract competition analysis; unvalidated <i>in vitro</i>
Olori et al. (2023)	<i>Hoslundia opposita</i> , <i>Cajanus cajan</i> phenolics	Virtual screening, QSAR; African Natural Products DB	HbS polymerization & cell gelation	Predicted: Phenylalanine derivatives bind HbS hydrophobic patch Validated: <i>In vitro</i> anti-sickling assay cross-confirmed	Limited to single compound models; lacks pharmacokinetic ADMET validation

Maturana-Pérez et al. (2024)	Multi-plant polyphenolic extracts	Network Pharmacology, PPI topology (Cytoscape); TCMS	Microvascular inflammation & endothelial adhesion	Predicted: Flavonoids target NF- κ B and adhesion cascades Validated: Retrospective literature correlation	Qualitative interaction nodes; lacks quantitative dose-response modeling
Chambhare et al. (2025)	<i>Guizotia abyssinica</i> terpenoids	ML classifiers, QSAR modeling	γ -globin expression/HbF induction	Predicted: Terpenoid scaffolds induce γ -globin expression Validated: Reporter gene assay in cultured cells	Cell-line model only; in vivo bioavailability unconfirmed
Ala et al. (2023)	Plant-derived small molecules	Structure-based screening, MD simulation; PDB: 4I9S	DNMT1/Epigenetic repressor inhibition	Predicted: Scaffolds bind DNMT1 catalytic domain to block HbF silencing Validated: None (<i>In silico</i> only)	Short MD simulation timescale; unconfirmed cellular toxicity
Gertsch J, 2011	<i>P. guineense</i> , <i>S. bicolor</i> , <i>E. caryophyllus</i> mixture	Compound-target network mapping, pathway enrichment	Dual action: HbS polymerization & membrane stabilization	Predicted: Polypharmacological synergy across multiple targets Validated: <i>In vitro</i> anti-sickling & clinical trial data	High batch -to-batch variation in wild-harvested raw materials

Comparative analysis demonstrates that different therapeutic endpoints within SCD require fundamentally distinct chemical scaffolds. Directly inhibiting HbS polymerization at the β 6 Val hydrophobic contact site requires rigid, hydrophobic, fused planar aromatic architectures (exemplified by benzophenanthridine alkaloids from *Zanthoxylum zanthoxyloides* and phenolics from *Hoslundia opposita*)⁶³. Conversely, epigenetic induction of fetal hemoglobin (γ -globin expression via DNMT1/HDAC inhibition) is governed by flexible, poly-hydroxyl functionalized scaffolds (such as terpenoids from *Guizotia abyssinica* and curcuminoids)^{58,64}. Computational screening pipelines must therefore avoid uniform filtering protocols and instead apply endpoint-tailored structural scoring matrices.

Workflows combining GNNs or QSAR filtering with Molecular Dynamics (MD) simulations performed significantly better, accurately accounting for

conformational flexibility and binding free energies (MM-GBSA/PBSA)⁶⁵. However, network pharmacology proved most useful for evaluating multi-component extracts, successfully resolving multi-target polypharmacology where single-ligand docking failed^{31,66}. Across the evaluated studies, three consistent, disease-specific findings emerge: scaffolds targeting direct HbS polymer disruption at the β 6 Val hydrophobic pocket require rigid, planar, fused aromatic ring systems (such as benzophenanthridine alkaloids)⁵⁵. In contrast, scaffolds targeting epigenetic HbF induction favor flexible, multi-hydroxyl functionalized terpenoids and flavonoids⁶³. Single-target screening models underrepresent the therapeutic potential of traditional extracts. Network pharmacology synthesis reveals that complex preparations like Niprisan® function through complementary nodes: alkaloid components directly impede polymer nucleation, while flavonoid glycosides mitigate oxidative lipid peroxidation and membrane fragility^{15,37}. Across the primary computational evidence

base, less than 30% of *in silico* predictions underwent prospective experimental validation (*in vitro* sickling assays or cellular models). Over 70% of computational predictions remain unvalidated by prospective experimental assays. This points to a systematic reliance on computational scoring functions trained on synthetic libraries, underscoring the need for prospective empirical cross-validation before pursuing clinical translation.

Future Challenges and Ethical Considerations

The growing use of computational tools to analyze ethnobotanical knowledge raises unresolved questions of governance, equity, and scientific method. As chemical, genomic, and traditional-use data move into digital repositories, the link between source communities and downstream research is changing. Value can now be derived from digital sequence information and chemical annotations without the physical collection of plant material⁶⁷. This shift complicates existing frameworks for access and benefit sharing. Agreements such as the Nagoya Protocol were developed around tangible biological samples, and their application to computational workflows is not straightforward⁶⁸. When algorithms generate synthetic analogs based on structures described in traditional contexts, tracing contributions and assigning benefits becomes difficult. Legal concepts of inventorship are still defined around human contributors, which can make the role of communities that developed and maintained knowledge over time less visible in formal records⁶⁸.

Equity in the data used to train models is a second issue. Many chemical and biological prediction tools rely on datasets that are skewed toward compounds studied in high-income countries⁶⁹. This can narrow the chemical space available to algorithms and reduce the likelihood that compounds unique to African or South Asian plants are identified and tested. Structures that fall outside standard drug-likeness rules may be deprioritized even if they have relevant biological activity. Patient data used to develop or validate models also tend to underrepresent populations where sickle cell disease is most common. If predictions are not assessed across the genetic and clinical diversity present in sub-Saharan Africa and South Asia, conclusions about safety and efficacy may not hold in those settings⁷⁰. Without attention to these gaps, computational approaches could reinforce rather than reduce disparities in access to new therapies.

There is also a conceptual difference between computational drug discovery and many traditional

systems of medicine. Early-stage algorithms usually rank individual compounds by binding or activity against a single target, reflecting a reductionist framework⁷¹. Traditional preparations are often mixtures, and their use is tied to specific practices around preparation, season, and administration⁷². These contextual factors are rarely captured in chemical databases or model inputs. Omitting them can create a gap between what is predicted computationally and what is observed in traditional use. Bridging this gap will require new ways to represent mixtures and associated variables in models, while maintaining the reproducibility that computational methods depend on. Collecting and curating such data will involve work with practitioners and communities to define what information is essential and how it can be recorded consistently.

Governance structures need to keep pace with these changes. Technical systems that record the origin of data and track its use can support more transparent benefit-sharing. Digital libraries of traditional knowledge with persistent identifiers and logs of access provide a way to document sources. If these systems are linked to agreements about benefit allocation, they could form a basis for arrangements when a digital record contributes to a downstream discovery. However, the effectiveness of such approaches depends on agreement about standards, interoperability, and how rules are applied across jurisdictions. Without shared norms, technical tools alone will not resolve questions of ownership or compensation.

Regulatory evaluation will also need adaptation. Agencies have established pathways for single-entity drugs, but multi-component botanical products require different approaches to characterization, quality control, and clinical assessment. Data from long-term traditional use can inform the design of studies and help define reasonable expectations for safety and activity, but they do not substitute for controlled trials. Developing criteria that combine mechanistic data from computational models with evidence from traditional practice could help create a clearer path for evaluation. This will involve consensus on what evidence is sufficient for complex mixtures and how to ensure consistency across batches and sources.

In the context of ethnopharmacology and AI-driven drug discovery, decolonization is operationally defined in this review as an ethical and regulatory framework that seeks to dismantle historical asymmetries in plant-derived research. It requires establishing data sovereignty, ensuring fair representation of endemic African and South Asian flora in public chemical databases, and enforcing equitable benefit-

sharing with Indigenous and local communities whose traditional knowledge generates initial drug leads.

The computational workflows reviewed here do not, in themselves, achieve decolonization. Rather, the digitizing of traditional knowledge into DSI and chemical SMILES notation creates new risks of biopiracy and exploitation if disconnected from source communities. AI models trained on Western-centric databases (such as ChEMBL or PubChem) frequently exhibit representation bias, deprioritizing unique natural scaffolds from endemic flora. Therefore, decolonizing SCD therapeutics requires implementing technical and legal mechanisms, such as persistent digital provenance tracking, open-access natural product repositories (e.g., the African Natural Products Database), and enforceable Nagoya Protocol benefit-sharing agreements before commercial translation⁷³.

While computational models can prioritize phytochemical leads and predict pharmacokinetic (ADMET) properties, they do not establish physical standardization, batch consistency, or regulatory validation⁷⁴. The reviewed evidence demonstrates that multi-component botanical preparations face severe quality control challenges due to seasonal, geographical, and chemodiversity variations in wild-harvested plants.

Current regulatory pathways (such as US FDA or WHO botanical guidelines) require rigorous fingerprinting, marker-compound quantification, and batch-to-batch reproducibility that cannot be solved by in silico docking alone³⁵. Computational predictions serve strictly as initial filtering mechanisms to select multi-target combinations; actual standardization remains an empirical prerequisite that demands standardized extraction protocols, chromatographic profiling (HPLC/LC-MS), and controlled clinical trials.

Rather than treating decolonization as an abstract theoretical goal, this review operationalizes it as a four-pillar regulatory and governance protocol required when handling ethnobotanical datasets: Digitized traditional knowledge must maintain explicit metadata tags linking plant scaffolds to source communities, requiring verifiable mutually agreed terms (MAT) prior to in silico screening. Open-access chemical and genomic databases must implement persistent digital identifiers (e.g., blockchain-based or FAIR-compliant DSI registries) to ensure raw phytochemical data from African and South Asian flora cannot be commercially patented without fair attribution. Translational pipelines must enforce binding ABS

agreements where downstream monetary and non-monetary benefits (e.g., tech transfer, local capacity building) return to Indigenous knowledge holders. AI models must actively incorporate regional repositories (such as the African Natural Products Database) to overcome Western-centric training dataset bias.

Recent literature proposes pairing AI drug discovery with multi-scale digital twins, local decentralized processing, and microbial biosynthesis¹⁶. However, synthesized evidence demonstrates that these advanced models face severe practical limitations: While computational models can theoretically simulate patient-specific responses to complex extracts based on genomic profiles (e.g., vaso-occlusive vs. hemolytic subphenotypes), zero clinical trials currently validate digital twins for botanical dosing in SCD. The high cost of multi-omics profiling limits near-term feasibility in low-resource settings⁶⁴. Establishing small-scale, standardized extraction facilities near endemic plant harvest sites is constrained by unreliable power grids, lack of ISO/IEC 17025-accredited analytical equipment, and capital expenditure limits. Without centralized regulatory oversight, batch variation remains a significant risk. Heterologous production of secondary metabolites in microbial hosts offers a solution to overharvesting. However, complex multi-gene biosynthetic pathways in species like *Zanthoxylum zanthoxyloides* remain incompletely mapped, making industrial fermentation cost-prohibitive compared to sustainable wild cultivation.

Finally, the composition of training and reference datasets needs attention. Reviewing datasets for geographic and chemical coverage can highlight where representation is lacking and guide efforts to expand collections. Collaboration between researchers, herbaria, and communities can improve the inclusion of African and Indian plant chemistry in public resources. Such efforts must be designed to respect consent and data rights and to ensure that communities participate in decisions about use. If diversity in data is not addressed deliberately, models will continue to reflect existing biases in global research.

Computational methods have expanded the ways ethnobotanical knowledge can be examined for sickle cell disease. Realizing their potential will depend as much on how governance, equity, and methodological questions are addressed as on improvements in algorithms or data volume. Addressing these governance and equity issues is as important as technical advances if computational approaches are to deliver benefits where the sickle cell disease burden is highest. Progress will depend on aligning scientific methods with agreements on data use,

representation, and benefit sharing that are developed with source communities.

A Roadmap for Decentralized, AI-Integrated SCD Care

Computational analysis of ethnobotanical data is beginning to move from laboratory studies toward models of care that can be applied closer to where patients live. For SCD, this shift depends on linking chemical predictions to clinical

practice in settings with limited infrastructure. The underlying idea is that traditional knowledge can suggest biologically relevant starting points, while computational methods can help define mechanisms, prioritize compounds, and generate data needed for evaluation (fig. 1). Bringing these elements together could support more locally available options for managing SCD, but several steps remain before such approaches become routine.

Integrated Translational Pipeline for Computational Ethnopharmacology in SCD

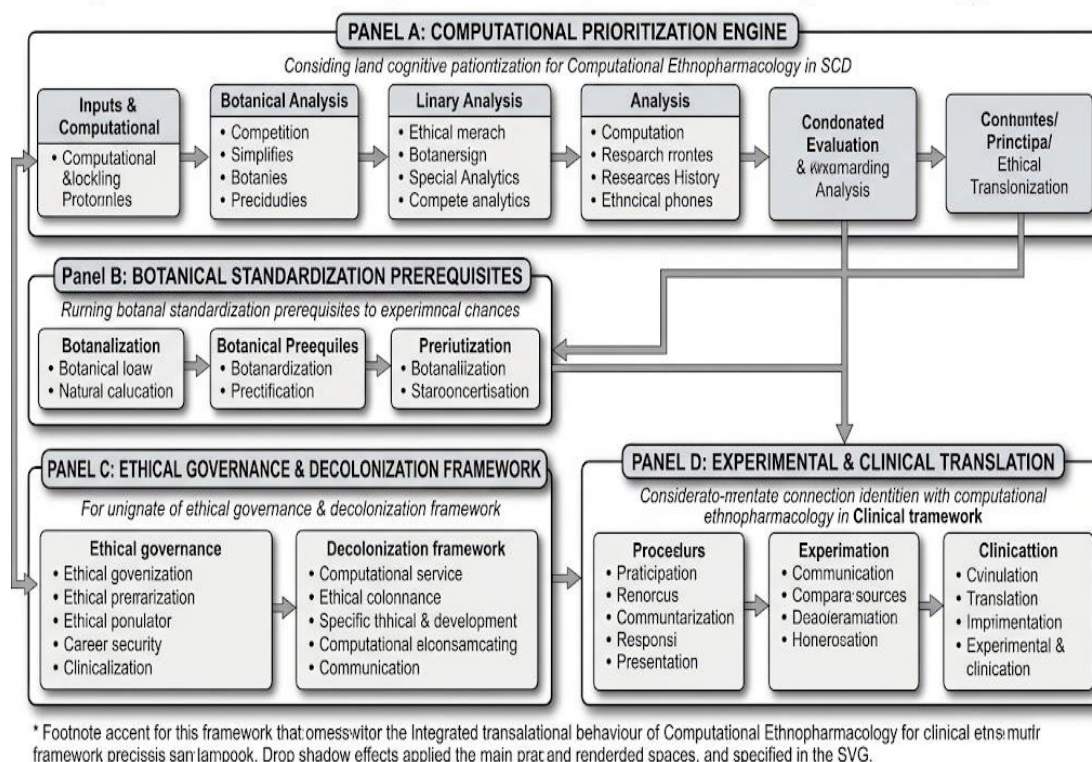


Figure 1. Integrated Pipeline for Computational Prioritization, Botanical Standardization, and Ethical Governance in SCD Ethnopharmacology. **A**, Computational Prioritization Engine: Illustrates data representations (SMILES, 3D conformers) processed through Graph Neural Networks (GNNs) and molecular docking against HbS (β6 Val pocket) and epigenetic targets. Network pharmacology maps multi-target synergy in extracts like *Niprisan*®, followed by in silico ADMET filtering to generate prioritized leads. **B**, Botanical Standardization Prerequisites: Outlines essential physical quality control steps required to translate computational leads, including DNA barcoding for plant authentication, HPLC/LC-MS chemical fingerprinting, marker compound quantification, and GMP manufacturing batch-consistency controls. **C**, Ethical Governance and Decolonization Framework: Details data sovereignty and equity mechanisms, including Indigenous community consent,

persistent identifiers for Digital Sequence Information (DSI), Nagoya Protocol benefit-sharing agreements, and local co-ownership of intellectual property. **D**, Experimental Translation: Connects prioritized, standardized leads to prospective *in vitro* sickling assays and clinical evaluation.

One direction is greater personalization of plant-based therapies. Computational models of patients, often called digital twins, can integrate clinical data, hemoglobin profiles, and molecular subphenotypes to simulate responses to specific compounds or mixtures²⁴. In SCD, distinguishing features such as a propensity for vaso-occlusion versus hemolysis may affect which biological processes are most relevant for a given individual⁷⁵. If models can predict how a particular extract influences HbF levels or erythrocyte stability for a specific profile, clinicians could use those predictions to select preparations

with a higher likelihood of benefit. The value of this approach will depend on validation with experimental and clinical data, and on agreement about how model outputs are interpreted alongside standard care.

Moving from prediction to clinical use will require staged development and evaluation. First, systems for recording and sharing ethnobotanical data need to be compatible with agreements on access and benefit sharing. Persistent records that link chemical and biological data to source information can support transparency and help communities participate in decisions about use. Second, computational simulations and in vitro studies can reduce the number of candidates taken into early clinical testing, which is particularly relevant for multi-component botanical products where standard trial designs are complex. Data from these studies can inform dose selection, safety monitoring, and endpoints. Third, regulatory pathways will need to accommodate products that combine historical use data with mechanistic evidence from computational and laboratory studies. Developing criteria for such products will involve coordination between researchers, regulators, and practitioners to define what evidence is sufficient for approval and post-market monitoring.

Sustainability of plant resources is another consideration. Demand for specific species could increase if compounds show clinical promise, which raises concerns about overharvesting. Computational methods can help identify biosynthetic pathways for active metabolites, and these pathways can be expressed in microbial systems for production without harvesting wild plants. This approach does not replace conservation of plant populations, but it can reduce pressure on them. In parallel, agricultural practices for medicinal plants can be informed by models that relate growing conditions to metabolite content. Adjusting soil, water, and harvest parameters based on these models may improve the yield of desired compounds while supporting cultivation rather than wild collection.

The development of this field also depends on training and collaboration. Researchers working at the intersection of computational science, pharmacology, and ethnobotany need skills that span data analysis, chemistry, and clinical context. At the same time, traditional practitioners hold knowledge about plant use, preparation, and patient observation that is not captured in databases. Recording and integrating this information requires tools that are accessible and respectful of local practice. When practitioners participate in data collection and

interpretation, the resulting hypotheses are more likely to reflect the complexity of traditional preparations and to be relevant to the communities where they are used.

Several gaps must be addressed before decentralized, AI-supported care for SCD is feasible at scale. Predictive models need broader chemical and patient diversity in training data to perform reliably across populations⁶³. Standards for characterizing multi-component products must be developed so that results from different sites can be compared. Agreements on data governance and benefit sharing must be in place and applied consistently. Technical solutions alone will not overcome these barriers; progress will require alignment between scientific work, regulatory development, and community engagement.

Computational methods have expanded the options for studying ethnobotanical knowledge relevant to SCD. Whether they translate into care models that improve outcomes will depend on how well technical development is matched by work on validation, equity, and implementation in the settings where need is greatest.

Realizing decentralized, AI-supported care for sickle cell disease will depend on validating computational predictions in clinical settings and ensuring that data, governance, and production systems are adapted to local conditions⁴⁶. If technical development is paired with equitable partnerships and rigorous evaluation, plant-derived therapies identified with computational tools could help address treatment gaps in the regions most affected by SCD.

Critical appraisal and limitations of AI-integrated ethnopharmacology

Computational approaches applied to ethnobotanical data for sickle cell disease show potential for hypothesis generation and compound prioritization. However, several methodological and systemic limitations constrain current applications and translation:

Most models are trained on databases dominated by synthetic, well-characterized small molecules. This limits generalization to the structural diversity and multi-component nature of plant extracts. Heterogeneous, multimodal biological data from ethnobotanical studies often lack standardized preprocessing and reporting formats, which reduces reproducibility across studies and laboratories.

AI models depend on large, high-quality datasets. Limited data on phytochemical activity, pharmacokinetics, and toxicity in African populations with high genetic diversity constrain model training and generalizability. This increases the risk of ineffective or unsafe dosing recommendations without experimental validation. Regions with high SCD prevalence often have limited laboratory infrastructure, fewer trained personnel, and challenges in data collection and standardization²¹. These constraints reduce the availability of representative datasets for model development and external validation.

In silico models often prioritize compounds based on binding affinity but cannot reliably predict in vivo pharmacokinetics, toxicity, or efficacy¹³. Regulatory evaluation of multi-component botanical formulations requires standardized chemical characterization, batch consistency, and safety testing, for which harmonized criteria are not yet established.

Many computational workflows are validated internally but lack external validation on chemically and clinically distinct datasets. Reliance on existing database associations can propagate errors and bias models toward pharmacologically plausible but experimentally unconfirmed predictions¹⁷. False-positive rates remain difficult to estimate without prospective experimental testing⁷⁰.

Deep learning and graph-based models frequently function as black boxes, providing predictions with limited mechanistic insight⁶⁵. In ethnopharmacology, regulatory and scientific evaluation of multi-component preparations requires evidence of constituent activity and interaction. Limited interpretability complicates assessment of synergy, antagonism, and safety.

Regulatory pathways for botanical products differ from those for single-entity drugs, and standardized criteria for evaluating AI-prioritized, multi-component formulations are not yet established. Requirements for chemical characterization, batch consistency, safety testing, and benefit-sharing add complexity to translation from in silico prediction to clinical development.

Progress depends on bias-aware frameworks that integrate experimentally acquired data, standardized reporting of plant material and assays, and models designed for interpretability. External validation and transparent reporting of limitations are required to move from computational hypothesis to experimentally and

regulatory-validated leads.

5. Conclusion

Sickle cell disease remains a major global health burden, particularly across sub-Saharan Africa and South Asia, where access to curative gene therapies is severely constrained by cost and specialized infrastructure requirements. While traditional health systems have relied on medicinal plants for generations, integrating ethnobotanical leads into evidence-based therapeutics requires systematic, molecularly defined evaluation.

This integrative review demonstrates that computational architectures, spanning graph neural networks, chemical language models, structure-based molecular docking, and multi-node network pharmacology, provide an effective framework for prioritizing natural product scaffolds, predicting multi-target mechanisms, and filtering pharmacokinetic properties in silico. By narrowing the vast chemical search space of plant extracts, these tools enable the formulation of testable, molecularly defined hypotheses to guide downstream experimental validation.

However, computational modeling represents an initial hypothesis-generation step in early discovery rather than an accomplished clinical solution. Realizing the actual translation of prioritized ethnobotanical candidates into standardized therapeutics depends on several essential prerequisites: In silico predictions must be systematically validated through prospective in vitro anti-sickling assays, enzyme kinetics, and controlled animal models. AI architectures require training on expanded databases that accurately capture the chemical diversity of endemic flora and the genetic diversity of patient populations in high-burden regions. Chromatographic chemical fingerprinting (HPLC-MS/MS), marker-compound quantification, and batch-to-batch consistency testing remain indispensable for regulatory approval. Equitable translation requires transparent benefit-sharing, Digital Sequence Information (DSI) data sovereignty, and Nagoya Protocol compliance to protect Indigenous knowledge holders.

Aligning computational prioritization engines with empirical validation, physical quality control, and ethical governance offers a pragmatic, defensible pathway toward expanding therapeutic options where the sickle cell disease burden is highest.

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