ISSN: 0976-7126
Dwivedi & Shrivastava, 16(11):5-10, 2025

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Integrative Ethnopharmacology of Indian Medicinal Plants for Sickle Cell Disease Management: Bridging Tradition with Evidence-Based Medicine

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Article info

Received: 11/09/2025

Revised:05/10/2025

Accepted: 25/10/2025

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Abstract

Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by polymerization of deoxygenated hemoglobin S (HbS), red blood cell (RBC) sickling, hemolysis, vaso-occlusion, and multi-organ complications. Conventional pharmacotherapy (e.g., hydroxyurea, L-glutamine, voxelotor) improves outcomes but remains costly, partially effective, and not universally available; moreover, many patients in low-resource settings rely on traditional medicine. Phytotherapeutic approaches — empirical herbal remedies and plant-derived bioactive compounds — have been studied for antisickling, antioxidant, membrane-stabilizing, and anti-inflammatory activities. India, with its rich ethnobotanical traditions, presents many candidate plants for SCD management.

This review synthesizes current knowledge on Indian medicinal plants with reported anti-sickling or supportive activities, summarizes common experimental models and mechanisms, evaluates the quality of evidence, and outlines research priorities for translating ethnobotanical leads into safe, standardized, and evidence-based phytotherapeutics.

Keywords: Sickle Cell Anemia, Medicinal Plants, Phytotherapy

Introduction

Sickle cell disease (SCD) affects millions worldwide and carries a heavy burden in parts of India, Africa, the Middle East, and among diasporic populations (Gonçalves et al., 2024). SCD pathology is driven by a single point mutation in the β-globin gene that favors polymerization of deoxygenated HbS, causing RBC deformation, vaso-occlusion, hemolysis, ischemia-reperfusion injury, and chronic inflammation. While disease-modifying drugs exist (e.g., hydroxyurea, voxelotor, crizanlizumab), access, cost, adverse effects, and incomplete efficacy drive interest in alternative and complementary approaches, especially in resource-limited settings (Gonçalves et al., 2024; Dash, 2013).

Medicinal plants have long been used empirically for SCD and SCD-related symptoms. Traditional healers have relied on whole plant extracts, mixtures, and processed formulations to reverse sickling or reduce crises. In some regions, standardized polyherbal products such as Nigeria's NIPRISAN (derived from indigenous species) were developed after ethnomedical leads and have shown clinical promise (Ameh, 2012). India's botanical diversity and traditional pharmacopoeias (Ayurveda, Siddha, tribal medicine) are potential reservoirs of antisickling agents.

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Over the past decades, numerous studies — primarily in vitro — have screened Indian and regionally available plants for antisickling activity, antioxidant capacity, membrane stabilization, and inhibition of HbS polymerization. This review collates evidence for Indian medicinal plants with potential relevance to SCD, outlines mechanisms and assay systems, and highlights gaps and future directions.

Ethnobotanical background and Indian relevance

Ethnobotanical surveys across regions endemic for SCD document widespread use of plants to treat anemia, pain crises, and general debility (Ameh, 2012; Dash, 2013). While many classical anti-sickling reports originated in African ethnomedicine (e.g., NIPRISAN derived from *Piper guineense*, *Pterocarpus osun* and *Harungana madagascariensis*), Indian ethnomedicine and recent Indian studies have explored local flora for anti-sickling potential. In tribal and rural parts of India, plants such as *Wrightia tinctoria*, *Terminalia arjuna*, *Terminalia bellirica*, *Rubia cordifolia*, *Moringa oleifera*, *Zanthoxylum* spp., and several other species have been tested for in vitro anti-sickling or membrane-stabilizing activity (Vaishnava & Rangari, 2019; Mishra et al., 2022; research from Madhya Pradesh and Chhattisgarh regions).

The Indian public health imperative is clear: affordable, locally sourced therapies that can complement conventional care would benefit large rural populations where access to modern SCD management is limited. Moreover, many Indian traditional practitioners report anecdotal improvements in clinical symptoms following specific herbal regimens, meriting systematic evaluation.

Commonly used Indian plants and experimental evidence

Numerous plants grown or used in India have been evaluated for antisickling and related properties. Below we summarize species with notable experimental support (in vitro / ex vivo or limited in vivo) and relevant findings.

Terminalia species (e.g., *Terminalia arjuna*, *Terminalia bellirica*)

Members of the Combretaceae (Terminalia spp.) have been studied for anti-sickling and antioxidant activities. Methanolic and aqueous extracts of *T. arjuna* and *T. bellirica* demonstrated in vitro anti-sickling activity in Emmel's tests and reduced hemoglobin S polymerization in some reports (Firodiya, Mani, & Thawani, 2017). The antioxidative polyphenols and tannins in Terminalia are plausible mediators of membrane stabilization and inhibition of oxidative damage to RBCs (Dash, 2013).

Moringa oleifera

Moringa oleifera (drumstick tree), cultivated widely in India, has antioxidant, mineral-rich, and membrane-stabilizing properties. In vitro work indicates that extracts of *M. oleifera* seeds and leaves can reduce sickling in deoxygenated HbS erythrocytes and offer antioxidant protection — possibly through zinc content and phenolic compounds (Omer et al., 2020; Adejumo et al., 2012).

Wrightia tinctoria

An Indian pharmacopoeial tree, *Wrightia tinctoria* extracts have been screened in regional Indian studies and shown promising anti-sickling activity in Emmel's tests (Vaishnava & Rangari, 2019). Phytochemicals including flavonoids and triterpenoids may underlie these effects.

Rubia cordifolia

Rubia cordifolia (Indian madder), used traditionally in Central India, was evaluated for anti-sickling, antioxidant, and anti-inflammatory activities in studies from Madhya Pradesh; methanol extracts displayed notable anti-sickling activity and antioxidant capacity (Mishra et al., 2022). Anthraquinones, flavonoids and other phenolics in *R. cordifolia* are candidate bioactives.

Zanthoxylum spp. and other Rutaceae

Zanthoxylum species have historical use as anti-sickling agents in several traditions. Isolated 2-hydroxybenzoic acid from *Zanthoxylum macrophylla* root extract was reported to possess anti-sickling activity (early phytochemical reports). Related species used in India show membrane stabilizing and anti-oxidative profiles (rural surveys; research journals).

Sorghum bicolor and related cereals

Sorghum varieties, used as diet or fermented mixtures traditionally, have been reported to contain phenolic fractions with antisickling activity. Studies have documented in vitro normalization of sickled cells after exposure to

certain Sorghum extracts, suggesting dietary adjunctive roles (recent Phyto studies).

Other plants reported in Indian screenings

Multiple Indian studies aiming to identify locally available anti-sickling leads have tested an array of species (e.g., *Wrightia tinctoria*, *Terminalia* spp., *Rubia cordifolia*, *Moringa oleifera*, species used in Chhattisgarh and nearby states) with varying degrees of in vitro success (Vaishnava & Rangari, 2019; Mishra et al., 2022). Many of these are preliminary, using ex vivo sickle blood samples, and emphasize the need for phytochemical characterization and standardization.

Mechanisms proposed for plant-mediated antisickling effects

Experimental and mechanistic studies propose several non-mutually exclusive mechanisms by which plant extracts may ameliorate sickling or its sequelae:

Inhibition of HbS polymerization — Certain phytochemicals may bind to hemoglobin or alter red cell milieu, reducing polymer formation during deoxygenation (Dash, 2013).

Membrane stabilization and osmotic protection — Flavonoids, saponins, and tannins can stabilize RBC membranes, reducing hemolysis and improving deformability (Dash, 2013; Mishra et al., 2022).

Antioxidant activity — Oxidative damage exacerbates sickling and hemolysis. Plant polyphenols, vitamins, and trace minerals (e.g., zinc) can scavenge reactive oxygen species (ROS), restore glutathione, and limit oxidative membrane injury (Adejumo et al., 2012; Omer et al., 2020).

Anti-inflammatory effects — Chronic inflammation is central in SCD pathophysiology; anti-inflammatory phytochemicals may moderate vaso-occlusive inflammation and endothelial activation (Mishra et al., 2022).

Improvement of rheological properties — Compounds that reduce cell aggregation or adhesion to endothelium, or that improve RBC deformability, may reduce vaso-occlusion (Dash, 2013).

Mineral and micronutrient supplementation — Plants rich in zinc, magnesium, or other co-factors might correct micronutrient deficiencies that worsen RBC fragility (Adejumo et al., 2012).

It is likely that many efficacious extracts exert multi-modal actions rather than a single molecular target, which aligns with the polyherbal approach of several traditional remedies.

Experimental models and assays used

Screening of plant extracts for anti-sickling or supportive activity employs several principal assays:

Emmel's test (visual sickling test) — An expedient ex vivo test where deoxygenation (e.g., via sodium metabisulfite) induces sickling in HbSS blood; reversal or prevention of sickling by extracts is observed microscopically. Many Indian in-vitro screenings use Emmel's test (Vaishnava & Rangari, 2019).

Polymerization inhibition assays — Measurement of HbS polymerization kinetics spectrophotometrically to assess the ability of extracts to slow or inhibit polymer formation (Dash, 2013).

Osmotic fragility and membrane stability tests — Evaluate RBC resistance to hypotonic lysis in presence of extracts (Mishra et al., 2022).

Antioxidant assays — DPPH, FRAP, TBARS, and glutathione assays quantify antioxidant potential of extracts, often correlated with antisickling capacity.

Red cell deformability and rheology tests — Ektacytometry and viscosity measures (less commonly used in basic screening but important for translational claims).

In vivo or clinical evaluations — Rare but critical; some polyherbal formulations (outside India) progressed to clinical observation (Ameh, 2012). Indian literature has few clinical trials; most data are preclinical.

Representative studies and outcomes

A number of reviews and primary studies document plant extracts with promising in vitro activities. Dash (2013) comprehensively reviewed antisickling agents from plants globally, highlighting species such as *Anacardium occidentale*, *Psidium guajava*, *Terminalia catappa*, and anthocyanin-rich species that exhibited inhibition of RBC sickling. Ameh (2012) reviewed traditional herbal management of SCD and summarized the development of therapies like NIPRISAN through systematic phytochemical research. Indian regional studies (e.g., Vaishnava & Rangari, 2019; Mishra et al.,

2022) screened local species such as *Wrightia tinctoria*, *Rubia cordifolia*, *Terminalia* spp., and reported significant in vitro antisickling and antioxidant activities in several extracts.

Moringa studies (Omer et al., 2020; Adejumo et al., 2012) demonstrated that leaves and seeds can reduce sickling and provide antioxidant benefits, possibly via zinc and phenolics. Sorghum and fermented mixtures historically used in diets and folk remedies have shown modulation of sickling in vitro, suggesting dietary interventions could be adjunctive (various phytochemical screens). More recent targeted chemical profiling (e.g., anthraquinones, phenolic acids, flavonoids) has identified candidate molecules for further SAR (structure-activity relationship) work (Mishra et al., 2022; Dash, 2013).

Quality of evidence and limitations

While many plant extracts show favorable in vitro data, several limitations hamper translation:

Predominance of in vitro/ex vivo data — Most Indian studies remain at screening stage (Emmel's test, polymerization inhibition), lacking downstream in vivo validation or randomized clinical trials.

Lack of standardization — Variability in plant part used, extraction solvent, methods, and lack of phytochemical standardization limit reproducibility.

Dose and safety data sparse — Toxicological profiling, chronic safety, and potential drug interactions (e.g., with hydroxyurea) are insufficient in the Indian literature.

Mechanistic ambiguity — While antioxidant and membrane-stabilizing roles are commonly invoked, molecular targets (e.g., hemoglobin binding sites) require rigorous biochemical validation.

Regulatory and quality control gaps — For clinical use, consistent Good Manufacturing Practice (GMP) production, stability data, and regulatory approval pathways are needed.

Thus, although ethnobotanical knowledge and initial screens present a promising pipeline, robust translational research is essential.

Integration with conventional therapy and potential clinical roles

Plant-derived interventions could serve several roles in SCD care:

Adjuncts to conventional therapy — Complement hydroxyurea and supportive care by reducing oxidative stress, improving RBC stability, and potentially reducing crisis frequency.

Symptomatic relief and supportive nutrition — Nutrient-rich plants (e.g., *Moringa*) may address malnutrition and micronutrient deficits that exacerbate SCD morbidity.

Affordable community-based therapies — For remote populations with limited access to modern drugs, validated phytotherapeutics might offer accessible supportive benefits.

Source of lead compounds — Isolation and chemical modification of bioactives may yield novel antisickling small molecules (for example, anthocyanins, phenolic acids) suitable for drug development.

However, integration requires clinical validation of efficacy and safety, and mechanisms for pharmacovigilance.

Safety, interactions, and ethical considerations

Natural does not equal safe. Some plant constituents can be toxic, teratogenic, or interact with pharmaceuticals (CYP enzymes, blood cell physiology). All prospective phytotherapeutics require rigorous toxicology, genotoxicity, and interaction studies. Ethical and biodiversity concerns (sustainable harvesting, benefit sharing with tribal communities) must be addressed, particularly when commercializing traditional knowledge (Ameh, 2012).

Research priorities and future directions

To translate Indian ethnobotanical leads into clinically useful interventions, the following priorities are proposed:

Standardized phytochemical profiling — Use HPLC, LC-MS/MS, NMR to identify active constituents and establish marker compounds for quality control.

Mechanistic biochemical studies — Elucidate direct hemoglobin interactions, polymerization inhibition kinetics, and molecular binding sites.

In vivo efficacy and toxicology — Test promising extracts/compounds in animal models for pharmacokinetics, pharmacodynamics, and chronic toxicity.

Formulation and delivery — Develop stable formulations (standardized extracts,

encapsulation) to ensure bioavailability and dosing precision.

Pilot clinical trials — Conduct well-designed Phase I/II trials to evaluate safety and efficacy as adjuncts to standard care.

Integration with nutritional interventions — Evaluate dietary approaches (e.g., sorghum formulations, Moringa supplementation) in cohort studies.

Sustainable sourcing and ethical frameworks — Ensure conservation, benefit-sharing, and community involvement.

Interdisciplinary collaborations — Bring together ethnobotanists, pharmacologists, hematologists, and regulatory experts.

Conclusion

India's rich botanical heritage contains many potential antisickling and supportive agents for SCD. Several indigenous plants—Terminalia spp., Moringa oleifera, Wrightia tinctoria, Rubia cordifolia, and related species—have shown promising in vitro antisickling, antioxidant, and membrane-stabilizing properties. However, most evidence remains preclinical; robust phytochemical standardization, mechanistic elucidation, in vivo validation, and clinical trials are needed before safe, evidence-based phytotherapeutics can augment conventional SCD management. Given the high disease burden and limited resources in many regions, validated plant-derived interventions could offer accessible adjunctive therapies and novel lead compounds for drug development. Responsible, ethically guided translational research can bridge traditional knowledge and modern hematology to improve outcomes for people living with SCD.

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Cite this article as:
Dwivedi S. and Shrivastava S. (2015). Integrative Ethnopharmacology of Indian Medicinal Plants for Sickle Cell Disease Management: Bridging Tradition with Evidence-Based Medicine. *Int. J. of Pharm. & Life Sci.,* 16(11):5-10.

Source of Support: Nil
Conflict of Interest: Not declared
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