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Systematic Review

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Nutritional Interventions Influencing Fetal Hemoglobin Response and Clinical Outcomes in Sickle Cell Disease: A Systematic Review

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Abstract

Background and objectives: Nutritional status and bioactive dietary compounds may influence the clinical course of sickle cell disease (SCD) and modify fetal hemoglobin (HbF) response to hydroxyurea (HU). Evidence suggests that micronutrients, amino acid therapies, antioxidants, and anti-inflammatory strategies can serve as adjuncts to HU, though their effects on HbF induction are not yet fully established. This systematic review evaluates the impact of nutritional interventions on HU-mediated HbF induction and key clinical outcomes in individuals with SCD.

Methods: A systematic search of PubMed, Scopus, the Cochrane Library, Google Scholar, and African Journals Online identified studies published between January 2018 and December 2025. Eligible studies included patients with SCD on HU receiving nutritional interventions. HbF was the primary outcome; vaso-occlusive crises (VOCs), hospitalization, and oxidative stress indices were secondary outcomes. Risk of bias was assessed using the Cochrane RoB 2 and Newcastle–Ottawa tools, and certainty of evidence was graded using GRADE. The review protocol was registered in PROSPERO (CRD420251268453), following PRISMA 2020 guidelines.

Results: Eighteen studies and contextual evidence sources were included, comprising randomized trials, observational/interventional studies, and selected contextual mechanistic or pharmacological evidence. L-glutamine showed the strongest evidence for reducing VOCs and hospitalizations. Omega-3 fatty acids provided evidence for reducing pain-crisis outcomes and improving oxidative or inflammatory markers, though HbF effects were inconsistent. Vitamin D improved vitamin D status, bone-related outcomes, muscle strength, and HRQoL, with limited direct impact on HbF. Arginine therapy reduced pain scores and hospital stays during crises. Nutritional rehabilitation with ready-to-use therapeutic food improved treatment feasibility in malnourished patients. Butyrate remained biologically plausible but lacked sufficient contemporary clinical validation, while micronutrient status and HU-treated cohort data were associated with hematologic indices, oxidative stress markers, or growth-related outcomes, with limited evidence for direct micronutrient-driven HbF improvement. Phytochemicals demonstrated *in vitro* benefits but lack clinical validation.

Conclusions: Nutritional interventions are promising adjuncts to HU therapy. The strongest evidence supports L-glutamine for reducing VOCs and hospitalizations, while omega-3 fatty acids may improve pain-crisis outcomes and oxidative or inflammatory markers. Nutritional rehabilitation is particularly relevant in resource-limited settings. Butyrate and phytochemicals remain experimental. Larger, well-designed trials are needed to clarify long-term benefits and nutrient–drug interactions.

Keywords: Sickle cell disease; Hydroxyurea; Fetal hemoglobin; Nutritional intervention; Antioxidants; Anti-inflammatory.

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Introduction

Sickle cell disease (SCD) remains a major public health challenge, particularly in sub-Saharan Africa, where prevalence and disease burden are highest.[1] It is characterized by recurrent vaso-occlusive crises, hemolysis, inflammation, and progressive organ damage.[2,3] Hydroxyurea (HU) is the cornerstone therapy due to its ability to induce fetal hemoglobin (HbF), which reduces sickling and improves clinical outcomes.[4,5] However, individual responses to HU vary widely, with some patients achieving optimal HbF induction and clinical benefit, while others show limited improvement. This variability has been attributed to genetic modifiers, treatment adherence, and environmental factors, but emerging evidence suggests that nutritional status may also play a critical role.[6–9]

Micronutrient deficiencies, including folate, vitamin B12, zinc, and vitamin D, are common among individuals with SCD and may impair erythropoiesis and exacerbate oxidative stress.[10] Omega-3 fatty acid supplementation has also been reviewed as a strategy for reducing VOC-related hospitalizations.[11] Recent nutritional and adjunctive evidence includes vitamin D3 supplementation, preclinical synthetic omega-3 fatty acid evidence, and real-world L-glutamine data, with reported benefits on supportive clinical outcomes, oxidative injury, and SCD-related complications.[12–14] Vitamin D-related approaches, functional foods, short-chain fatty acids, pharmacological HbF-inducing strategies, and omega-3 fatty acids have been explored as supportive or mechanistic approaches in SCD, although direct HbF effects remain uncertain.[15–20] In addition, emerging evidence from clinical and real-world studies indicates that amino acid–based therapies such as L-glutamine and L-arginine may reduce SCD-related complications, pain outcomes, hospitalization, or hemolysis markers, highlighting their role in modulating disease severity independent of HbF response.[21–23]

Nutritional status also influences treatment tolerance and clinical outcomes in vulnerable populations. Studies in resource-limited settings and current HU treatment literature have highlighted that HU use in children with SCD can be feasible but may be affected by access barriers, safety monitoring, and supportive-care capacity.[24–26] Antioxidant strategies, including N-acetylcysteine, have been explored for reducing oxidative stress in SCD.[27] Omega-3 fatty acid supplementation has shown potential benefits in reducing pain-crisis outcomes and improving oxidative or inflammatory markers, although its effect on HbF induction remains inconsistent across studies.[20,28] Vitamin D status has also been associated with oxidative stress and supportive clinical outcomes in children with SCD.[29] Given the growing body of evidence, this systematic review aims to clarify the role of nutrition as a modifier of HU response, identify interventions with the strongest clinical support, and highlight gaps requiring further investigation.

Materials and methods

Search strategy

A comprehensive literature search was conducted across PubMed, Scopus, the Cochrane Library, Google Scholar, and African Journals Online for studies published between January 2018 and December 2025. The search string included a combination of the following keywords: ("sickle cell disease" OR "sickle cell disorder") AND ("hydroxyurea") AND ("fetal hemoglobin" OR "HbF") AND ("nutrition" OR "micronutrient" OR "antioxidant" OR "phytochemical" OR "butyrate" OR "amino acid" OR "omega-3"). Search strategies were adapted for each database, with field tags and subject headings modified accordingly. The study protocol was registered with PROSPERO (ID: CRD420251268453) following PRISMA 2020 guidelines, and key items were prospectively specified in the PROSPERO registration.

Eligibility criteria

Studies evaluating HU alone were included as baseline comparators for interpreting adjunctive nutritional effects. Interventions of interest included micronutrient supplementation (folate, vitamin B12, zinc, vitamin D, selenium); dietary bioactive compounds (butyrate, phytochemicals, nutraceuticals); amino acid–based therapies (L-glutamine, L-arginine); nutritional rehabilitation strategies; and antioxidant or anti-inflammatory approaches (omega-3 fatty acids, vitamins C and E, glutathione precursors). The primary outcome was HbF concentration, while secondary outcomes included vaso-occlusive crises, hospitalization, pain-related outcomes, growth indices, hematologic parameters, and oxidative stress markers. Eligible study designs included original clinical studies for the clinical evidence synthesis. Selected mechanistic/preclinical or non-nutritional pharmacological studies were retained only as contextual evidence when relevant to intervention mechanisms or VOC-management comparators. Review articles were used for contextual discussion and were excluded from evidence tables.

Exclusion criteria

Studies excluded from selection included those without confirmed SCD, those that did not report the use of HU, those that did not evaluate nutritional or dietary bioactive compound interventions, and those that did not report HbF or other relevant clinical outcomes such as vaso-occlusive crises, hospitalization, or oxidative stress markers. Additional exclusions from the clinical evidence synthesis included case reports, editorials, reviews, animal studies not retained as contextual mechanistic evidence, non-English articles, and duplicate publications of the same study.

Study selection

A total of 1,200 records were identified (Fig. 1). After the removal of duplicates (n = 375), 825 records were screened by title and abstract. Of these, 730 were excluded for not meeting the inclusion criteria (non-SCD populations, no HU use, non-nutritional interventions, or non-original data). The full texts of 95 articles were assessed, with 77 excluded for reasons including incorrect study design (n = 25), lack of HU co-treatment, absence of HbF or relevant clinical outcomes, and overlapping populations (n = 52). In total, 18 studies and contextual evidence sources, including 6 randomized controlled trials and 12 observational, interventional, preclinical, or contextual studies, were included in the qualitative synthesis (Tables 1 and 2; Figs. 2 and 3).[5–7,12–15,20,22–24,26,28–33]

Data extraction and risk of bias

Two reviewers independently screened titles, abstracts, and full texts against the inclusion criteria. Disagreements were resolved through consensus with a third reviewer. A

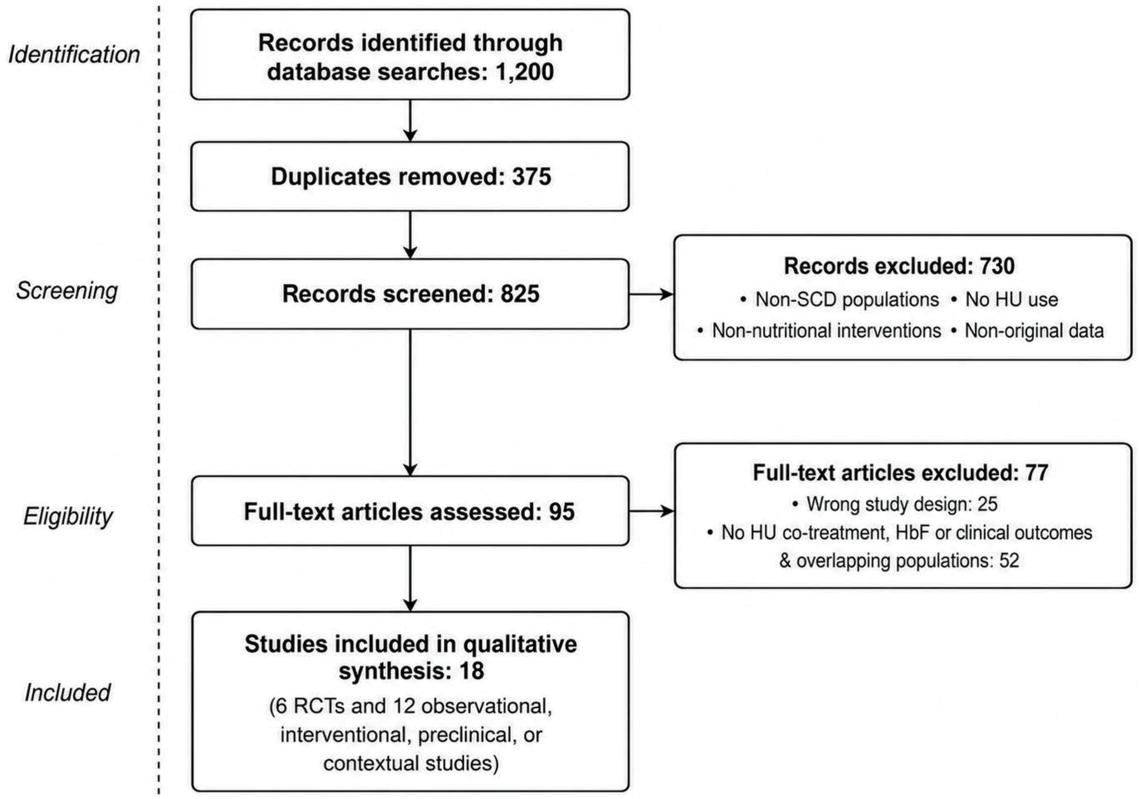

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram. HbF, fetal hemoglobin; HU, hydroxyurea; RCT, randomized controlled trial; SCD, sickle cell disease.

standardized form was used to extract study characteristics, including country, design, sample size, intervention, comparator, and outcomes. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool for randomized controlled trials and the Newcastle–Ottawa Scale for observational studies. Evidence certainty was graded using the GRADE framework.

Data synthesis

Given the heterogeneity in intervention types, dosing regimens, follow-up durations, and measured outcomes, a formal meta-analysis was not performed. Instead, findings were synthesized narratively by intervention category and outcome type. Certainty of evidence was summarized across interventions, ranging from moderate for L-glutamine and omega-3-related clinical outcomes to very low for phytochemicals.

Results

Characteristics of included studies

Eighteen studies and contextual evidence sources, including 6 randomized controlled trials and 12 observational, interventional, preclinical, or contextual studies, were summarized. The clinical studies comprised pediatric and adult patients with SCD from Africa, the Middle East, and North America, with contextual evidence from Europe and multi-country pharmacological studies. Sample sizes ranged from small pilot trials ($n \leq 40$) to large multicenter randomized trials ($n \geq 300$), with follow-up durations between 6 weeks and 48 months. HU was administered at standard dosing (generally 15–25 mg/kg/day, where reported), and nutritional interventions included micronutrients (folate, vitamin B12, vitamin D, zinc, selenium) (Table 3); amino acid–based therapies (L-glutamine, L-arginine); omega-3 fatty acids; short-chain fatty acids (butyrate); antioxidant vitamins (C and E); glutathione precursors; phytochemical extracts (Table 4); and nutritional rehabilitation strategies such as RUTF.

Several studies demonstrated clinically meaningful reductions in vaso-occlusive crises and improvements in hematologic or inflammatory markers. L-glutamine therapy, evaluated in both interventional and real-world settings, consistently reduced pain crises, hospitalizations, and transfusion requirements.[14,22] Omega-3 fatty acid supplementation was associated with pain-crises outcomes and improved oxidative or inflammatory markers, although its effect on HbF remained inconsistent.[20,28] Vitamin D3 supplementation improved vitamin D status, BMD, hand-grip strength, and HRQoL in pediatric SCD populations, while vitamin D status was also associated with oxidative stress markers; evidence for direct HbF effects remained limited.[7,12,15,29] Arginine therapy was associated with reduced pain scores, shorter time to crisis resolution, and decreased hospital stay during vaso-occlusive episodes.[23] Nutritional rehabilitation with RUTF was feasible and improved treatment tolerance in malnourished children receiving HU.[30] Detailed study char-

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Table 1. Characteristics of included studies

Author/Year	Country	Design	Sample size	Intervention	Comparator	Primary outcome	Secondary outcomes	Key findings
Mvalo *et al.*, 2019[26]	Malawi	Prospective cohort	187	Hydroxyurea therapy	Pre-treatment baseline	Improvement in HbF	Hospitalizations, vaso-occlusive events, safety and feasibility	Hydroxyurea improved hematologic parameters and reduced clinical complications, demonstrating feasibility of hydroxyurea therapy in a resource-limited setting
Khan *et al.*, 2022[20]	Saudi Arabia	Pilot interventional study	43	Omega-3 fatty acid supplementation	Baseline	Vaso-occlusive crisis frequency	Hematologic parameters, inflammatory markers	Reduced VOCs; improved erythrocyte stability
Mattè *et al.*, 2024[13]	Italy	Preclinical animal study	Mouse model	Epeleuton (synthetic ω-3)	Control group	Hypoxia/reperfusion-related oxidative stress	Sickle-related oxidative injury markers	Reduced oxidative injury in a mouse model; considered as preclinical contextual evidence
Elenga *et al.*, 2022[22]	Qatar & French Guiana	Prospective cohort study	19	Oral L-glutamine	Baseline	VOC frequency	Hospitalizations, blood transfusions, hemoglobin and hemolysis markers	Reduced crises and hospitalizations; improved hemolysis
Turkistani *et al.*, 2025[14]	Saudi Arabia	Retrospective cohort	200	L-glutamine + HU	HU alone	VOC frequency	Hospitalization, HbF	Real-world benefit confirmed; reduces VOC
Honhar *et al.*, 2024[15]	USA	RCT	60	High-dose of vitamin D (Stoss)	Placebo	Pain episodes/VOC	Vitamin D level, inflammatory markers	Improved vitamin D status; fewer crises
Onalo *et al.*, 2021[23]	Nigeria	Randomized double-blind RCT	68	Oral L-arginine	Placebo	Analgesic requirement during VOC	Pain scores, hospital stay	Reduced pain and hospital duration
Dampier *et al.*, 2023[32]	Multi country	Phase III RCT	345	Rivipansel, a non-nutritional pharmacological intervention	Placebo + standard care	Time to VOC resolution	Opioid use, hospital stay	No significant primary endpoint benefit; considered only as contextual pharmacological evidence for VOC management
Abdullahi *et al.*, 2023[30]	Nigeria	Multicenter RCT (feasibility)	110	RUTF + HU	RUTF alone	Nutritional recovery (BMI Z-score)	Safety adherence, hematologic response	Feasible and safe; improved nutrition

(continued)

Table 1. *(continued)*

Author/Year	Country	Design	Sample size	Intervention	Comparator	Primary outcome	Secondary outcomes	Key findings
Abdelhalim *et al*., 2022[28]	Egypt	RCT	165	Omega-3 fatty acids	Standard care	VOC frequency	Hematologic parameters, hospitalization rate	Reduced VOC and improved hematology
Hanna *et al*., 2024[12]	Multi-country	RCT	42	Vitamin D_3 supplementation	Placebo	Serum vitamin D level	Bone mineral density (BMD), hand-grip strength (HGS), health-related quality of life (HRQoL)	Improved vitamin D, BMD, QoL
Kalibbala *et al*., 2025[31]	Uganda	Prospective cohort	264	Hydroxyurea therapy	Age-standard reference	Growth parameters	HbF, clinical outcomes	Improved growth trends
Sonuga *et al*., 2025[29]	Nigeria	Case-control study	200	Vitamin D status	Healthy controls	Oxidative stress biomarkers	Antioxidant enzyme activity	Vitamin D linked to antioxidant status
Zahran *et al*., 2020[33]	Egypt	Prospective clinical study	60	Hydroxyurea	Baseline	Change in HbF(%)	VOC frequency, inflammatory markers	Increased HbF and reduced VOC
Ambrose *et al*., 2023[24]	Tanzania	Retrospective cohort	87	Hydroxyurea therapy	Baseline	VOC frequency	Hospitalization, transfusion, Hb, MCV	Reduced VOC and admissions
Emuli *et al*., 2025[6]	Uganda	Cohort	120	Hydroxyurea therapy	Baseline / treatment duration comparison	Hematologic improvement	HbF, micronutrient status	Hydroxyurea was associated with improved hematological indices
Adegoke *et al*., 2018[7]	Nigeria/ Brazil	Cohort	100	Hydroxyurea exposure	HU-naive or non-HU group	Growth parameters	HbF, vitamin D level	HU was associated with anthropometric outcomes, while vitamin D deficiency persisted
Owusu–Poku *et al*., 2022[5]	Ghana	Cohort	150	Micronutrients status and oxidative stress biomarkers	Not applicable / comparison by biomarker status	Oxidative stress biomarkers	HbF, clinical outcomes	Micronutrient and oxidative stress biomarkers were associated with HbF and disease-related parameters

BMD, bone mineral density; BMI, body mass index; Hb, hemoglobin; HbF, fetal hemoglobin; HGS, hand-grip strength; HRQoL, health-related quality of life; HU, hydroxyurea; MCV, mean corpuscular volume; RCT, randomized controlled trial; RUTF, ready-to-use therapeutic food; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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Table 2. GRADE summary of findings for nutritional interventions adjunctive to hydroxyurea

Outcome	No. of studies	Study design	Effect	Certainty of evidence	Interpretation
HbF increase	6	Cohort + RCT	Effects modest and inconsistent; micronutrient effects were limited, and butyrate remained biologically plausible but lacked sufficient contemporary clinical validation	Low–Moderate	Evidence is insufficient to confirm enhanced HU-mediated HbF response
VOC reduction	5	RCT + observational	Consistent evidence for L-glutamine; omega-3, vitamin D, and arginine showed supportive evidence for reducing pain-crisis or VOC-related outcomes	Moderate	Adjuncts reduce crisis frequency
Hospitalization	4	Cohort + RCT	L-glutamine reduced hospitalizations; RUTF improved tolerance; supportive outcomes noted	Low–Moderate	Evidence promising but heterogeneous
Hematologic improvement	6	Mixed designs	Micronutrient status and HU-treated cohort data were associated with hematologic indices, oxidative stress markers, or growth-related outcomes	Moderate	Likely benefit
Oxidative stress biomarkers	3	Observational	Micronutrients and antioxidant strategies, including NAC, improved oxidative stress markers	Low	Limited evidence
Growth / nutritional recovery	2	Cohort + RCT	RUTF improved treatment feasibility and nutritional recovery in malnourished children	Low	Limited evidence
Butyrate (HbF induction)	2	Mechanistic/ contextual evidence	Butyrate has biologically plausible HbF-inducing potential, but eligible contemporary clinical evidence was limited	Low	Experimental; clinical validation needed
Phytochemicals	several	*In vitro*	*In vitro* antisickling/antioxidant effects; no clinical validation, very low certainty	Very Low	Clinical validation lacking

HbF, fetal hemoglobin; HU, hydroxyurea; NAC, N-acetylcysteine; RCT, randomized controlled trial; RUTF, ready-to-use therapeutic food; VOC, vaso-occlusive crisis.

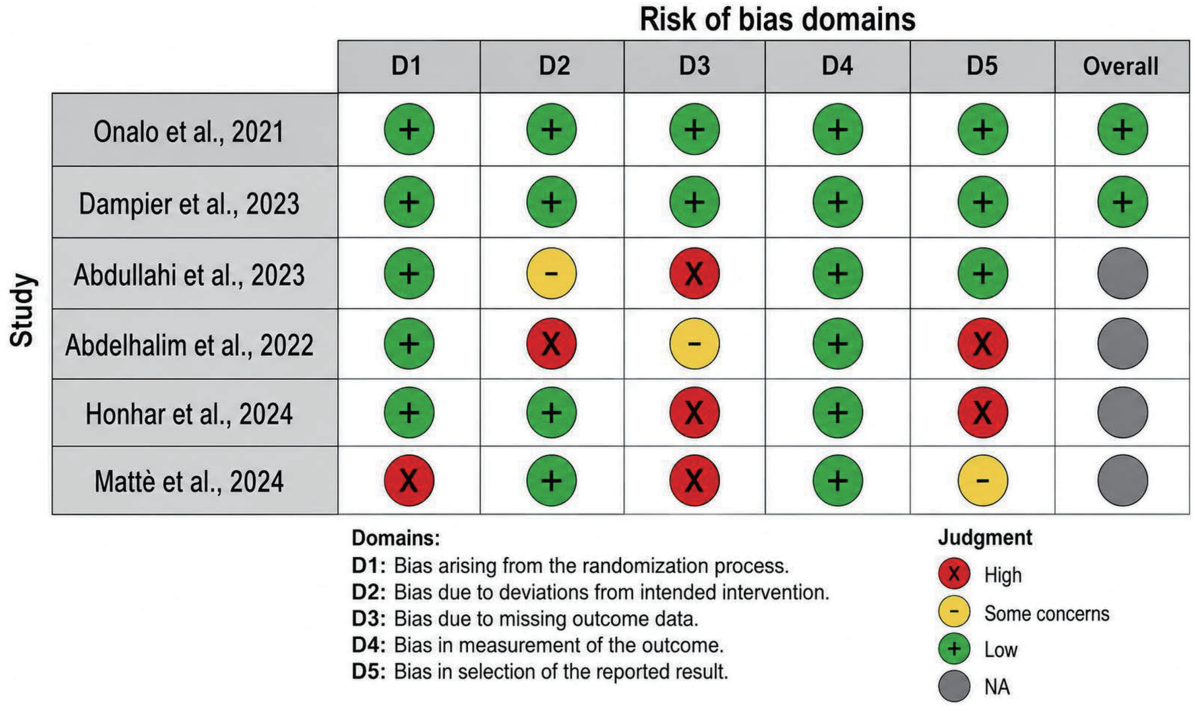

Fig. 2. Risk of bias assessment for randomized controlled trials (Cochrane RoB 2).

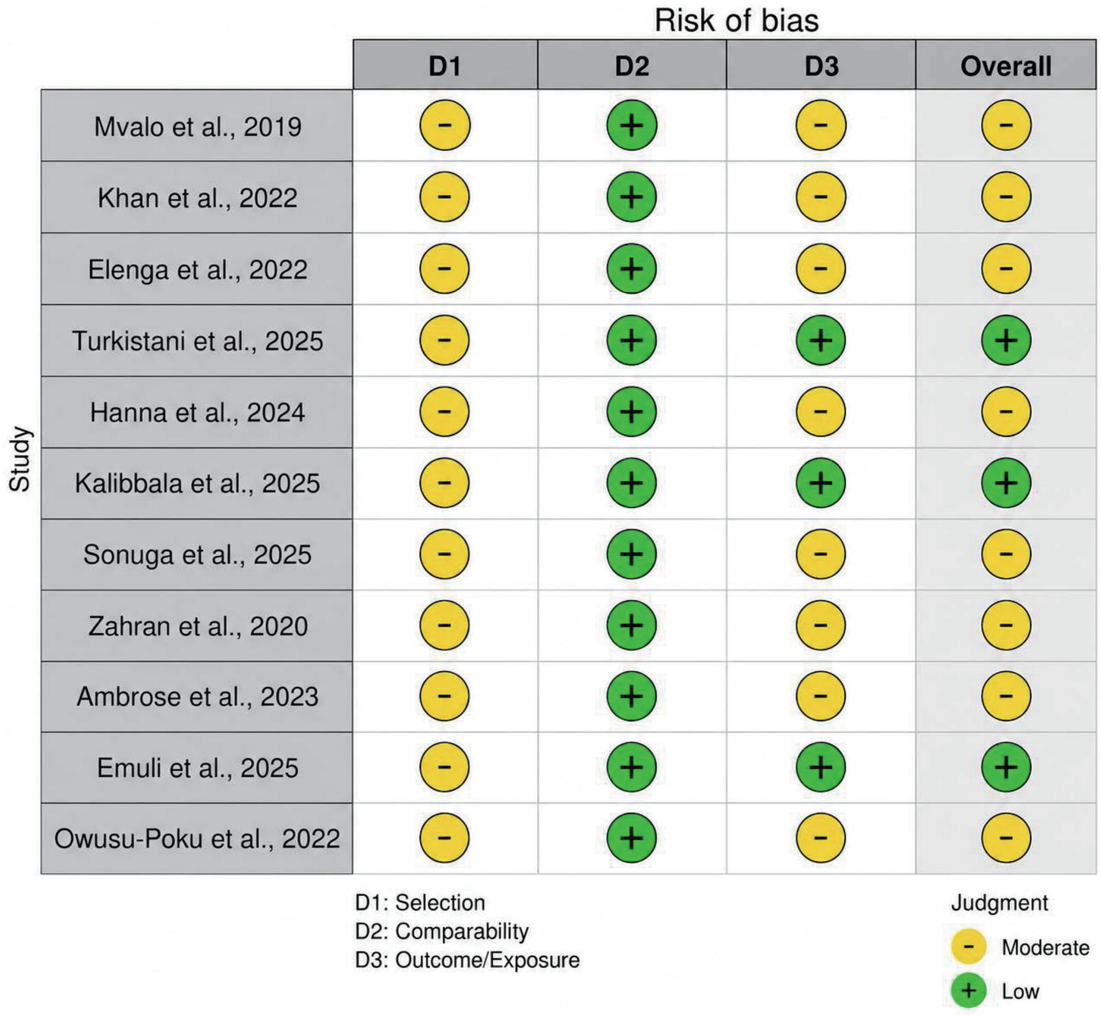

Fig. 3. Risk of bias assessment for observational studies.

acteristics are presented in Table 1.

Risk of bias

Among the randomized controlled trials, the overall risk of bias varied across studies. Onalo *et al.*[23] demonstrated low risk across most domains, while Abdullahi *et al.*[30] and Abdelhalim *et al.*[28] showed some concerns or higher risk in specific domains, particularly relating to deviations from intended

Table 3. Micronutrients and their impact on HU therapy and HbF induction

Micronutrient	Prevalence in SCD	Known impact on SCD	Potential impact on HU/HbF	Evidence level
Folate (B9)	Common	Required for DNA synthesis and erythropoiesis	HU-induced macrocytosis can mask deficiency	Observational / clinical consensus
Vitamin B12	Common	Cofactor for DNA synthesis and RBC formation	HU macrocytosis complicates diagnosis	Observational
Vitamin D	Very common	Bone health, muscle growth, pain modulation	No clear direct effect on HU response	Observational / small trials
Zinc	Prevalent	Immune function, antioxidant defense, growth	Potential indirect effect on HU pharmacokinetics	Small trials / observational
Iron	Variable	Essential for hemoglobin synthesis	HU may alter iron utilization	Observational / mixed data

DNA, deoxyribonucleic acid; HbF, fetal hemoglobin; HU, hydroxyurea; RBC, red blood cell; SCD, sickle cell disease.

Table 4. Roles of bioactive compounds in the management of SCD

Compound/Source	Type	Reported effects	Proposed mechanism	Evidence level
Butyrate	Short-chain fatty acid	HbF induction	Increases γ-globin expression	Mechanistic/contextual; clinical validation limited
Solenostemon monostachyus extract	Phytochemical	Antisickling	Transcriptional modulation (not fully understood)	*In vitro*
Carica papaya extract	Phytochemical	Antisickling & reduced hemolysis	Mechanism unclear	*In vitro*
Moringa oleifera extract	Phytochemical	Antisickling & antioxidant	Multitarget antioxidant and anti-inflammatory	*In vitro*
Nigella sativa oil	Phytochemical	Antisickling; antioxidant	Calcium antagonist & antioxidant effects	*In vitro*
Flavonoids	Polyphenols	Antisickling, antioxidant, anti-inflammatory	Membrane stabilization & ROS reduction	*In vitro*
Glutathione precursors	Amino acid derivatives	Improved RBC flexibility & reduced oxidative stress	Reduce ROS and endothelial adhesion	Clinical trials

HbF, fetal hemoglobin; RBC, red blood cell; ROS, reactive oxygen species; SCD, sickle cell disease.

interventions, missing outcome data, and selective reporting (Fig. 2). Mattè *et al*.[13] was not included in the clinical RCT risk-of-bias interpretation because it provided preclinical contextual evidence.

For observational studies, risk of bias assessment using the Newcastle–Ottawa Scale indicated predominantly moderate risk, with most studies showing adequate comparability but some concerns in selection and outcome assessment domains. A smaller number of studies demonstrated lower risk where study design and outcome ascertainment were robust, while others had unclear risk due to limited reporting of confounding control (Fig. 3).[24,26,29]

Certainty of evidence (GRADE)

The certainty of evidence ranged from moderate for L-glutamine to very low for phytochemicals (Table 2).[9,10,14,22] L-glutamine consistently reduced the frequency of vaso-occlusive crises across study designs, with minimal heterogeneity. Omega-3 fatty acids demonstrated evidence for reducing pain-crisis outcomes and improving oxidative or inflammatory markers, though effects on HbF remained inconsistent.[20,28] Vitamin D supplementation showed moderate-certainty evidence for improving supportive clinical outcomes, including bone health and quality of life, but limited direct impact on HbF.[7,12,15,29]

Amino acid–based therapies such as L-arginine demonstrated beneficial effects on pain-related outcomes,[23] though the evidence remains limited and was graded as low to moderate certainty due to fewer studies. Nutritional rehabilitation strategies showed promising clinical utility in improving treatment tolerance in resource-limited settings, though certainty remains low due to limited data.[30] Butyrate remained biologically plausible for HbF induction based on mechanistic and contextual evidence, but eligible contemporary clinical evidence was limited.[8,17,18] Micronutrient status and HU-treated cohort data were associated with hematologic indices, oxidative stress markers, or growth-related outcomes, but evidence for direct micronutrient-driven HbF improvement remained limited.[5,6,31] Phytochemicals and nutraceuticals demonstrated antisickling and antioxidant properties *in vitro* but lacked clinical validation, resulting in very low certainty of evidence.[9,10]

Discussion

This systematic review highlights the potential role of nutritional interventions as adjuncts to HU therapy in SCD. Across the studies included in this review, micronutrient deficiencies were consistently reported. Correction of deficiencies in folate, vitamin B12, zinc, and vitamin D improved general health outcomes, but there was limited evidence associating these interventions with direct modulation of HbF. For instance, Owusu-Poku *et al*.[5] demonstrated that micronutrient status and oxidative stress biomarkers interact with HbF levels in children with SCD, while Emuli *et al*.[6] showed improved hematological indices after one year of HU therapy, though HbF effects remained modest. These findings suggest micronutrient supplementation as supportive care rather than a primary driver of HbF induction.

Butyrate remains a biologically plausible HbF-inducing strategy via epigenetic mechanisms. However, much of the supporting evidence is mechanistic or contextual rather than derived from contemporary eligible clinical trials.[17,18] Therefore, butyrate should be regarded as experimental, and future studies should address its feasibility, dosing route, adherence, and potential role alongside HU.[8]

Antioxidant and anti-inflammatory strategies showed consistent benefits in reducing vaso-occlusive crises and improving red cell indices. Omega-3 fatty acids were associated with reduced pain-crisis outcomes and improved oxidative or inflammatory markers, though their effects on HbF were variable.[20,28] L-glutamine demonstrated evidence for reducing crises and hospitalizations, with findings supported by clinical and real-world studies.[14,22] Amino acid–based therapies such as L-arginine further demonstrated significant reductions in pain scores, time to crisis resolution, and hospital stay, indicating clinically meaningful benefits independent of HbF modulation. Antioxidant strategies, including

N-acetylcysteine,[27] improved oxidative stress markers, but their effects on HbF remained inconsistent. These observations highlight the importance of addressing oxidative stress and inflammation, which contribute to disease severity and variability in HU response.[3,33]

Phytochemicals and nutraceuticals such as Moringa, Nigella, and papaya extracts were discussed in Bell *et al*.[9] and Saha *et al*.[10] While *in vitro* studies demonstrated antisickling and antioxidant effects, clinical validation was lacking. Consequently, phytochemicals were rated as very low certainty. Their potential remains largely theoretical until robust clinical trials are conducted. Nutritional status also influences treatment tolerance and overall clinical outcomes. Evidence from feasibility trials in resource-limited settings demonstrated that nutritional rehabilitation strategies, including RUTF, improved treatment feasibility, safety, and nutritional recovery in children receiving HU.[30] This highlights the importance of addressing underlying malnutrition as part of comprehensive SCD management, particularly in high-burden regions.

Risk-of-bias assessment revealed variability in methodological quality across studies. While some randomized controlled trials demonstrated low risk of bias, others showed concerns related to deviations from intended interventions, incomplete outcome data, and selective reporting.[23,28,30] Observational studies were largely at moderate risk due to limitations in controlling for confounding factors and variability in outcome assessment.[24,26,29] Overall, these methodological limitations should be considered when interpreting the strength of evidence across interventions.

Substantial heterogeneity was observed across interventions, dosing strategies, and outcome definitions. For example, HbF was reported in different units and thresholds, while vaso-occlusive crises and pain outcomes were variably defined across studies. This heterogeneity limited direct comparability and precluded formal meta-analysis, necessitating a narrative synthesis. Nonetheless, the clinical signal for L-glutamine and omega-3 fatty acids in reducing crises, together with mechanistic and contextual evidence for butyrate or related bioactive compounds, supports their prioritization in future trials.[8,13,14,17,18,20,22,28]

Clinical implications

Nutritional assessment should be included as part of routine care for patients with SCD receiving HU. Screening for deficiencies in folate, vitamin B12, zinc, and vitamin D is important due to their involvement in erythropoiesis, oxidative stress, and potential modulation of HU response. Correcting deficiencies improves overall health, though HbF effects are limited. Among adjunctive strategies, L-glutamine has the strongest evidence for consistently reducing vaso-occlusive crises and hospitalizations. Omega-3 fatty acids show moderate evidence for reducing crises and improving oxidative stress, though effects on HbF are inconsistent. Vitamin D supports vitamin D status, bone-related outcomes, muscle strength, and HRQoL, particularly in pediatric and deficient populations. Arginine-based therapies may be beneficial in acute pain management during vaso-occlusive crises. Nutritional rehabilitation strategies are particularly relevant in malnourished populations, where they improve treatment feasibility and outcomes. Butyrate remains experimental due to feasibility constraints, and phytochemicals should be restricted to research settings until clinical evidence is available.

Limitations

This review has some limitations that affect interpretation of the findings. Many of the included trials had small sample sizes and short follow-up periods, reducing statistical power and limiting conclusions on the long-term effects of nutritional interventions on HU response. The outcomes measured were heterogeneous, with HbF reported in varying units, vaso-occlusive crises and pain outcomes defined inconsistently, and oxidative stress markers assessed using different methods, making comparisons difficult. The applicability of results is also constrained by the populations studied, as most trials were conducted in relatively well-nourished cohorts from higher-income settings, which may not reflect patients from resource-limited regions with different nutritional status, dietary patterns, and genetic modifiers. Methodological concerns were evident, with several studies judged at moderate to high risk of bias due to confounding and incomplete data, leading to variation in evidence certainty across interventions. Finally, publication bias remains possible, as smaller trials of micronutrients, amino acid therapies, and phytochemicals may be underreported, and positive findings are more likely to be published, potentially exaggerating benefits for low-certainty interventions.

Conclusions

Nutritional interventions represent biologically plausible and clinically relevant adjuncts to HU therapy in SCD. Among available strategies, L-glutamine consistently reduces vaso-occlusive crises and hospitalizations, while omega-3 fatty acids may improve pain-crisis outcomes and oxidative or inflammatory markers. Vitamin D supports vitamin D status, bone-related outcomes, muscle strength, and HRQoL, particularly in children. Nutritional rehabilitation enhances treatment tolerance in malnourished populations. In contrast, butyrate and phytochemicals remain experimental due to low-certainty evidence and feasibility challenges, and micronutrient status appears relevant to supportive clinical and oxidative stress-related outcomes, but current evidence does not show clear direct HbF induction. Routine nutritional assessment and targeted supplementation should be integrated into comprehensive SCD management, with priority given to interventions supported by stronger evidence. Future research should focus on large, well-powered trials in high-burden regions, standardized outcome measures, and nutrient–drug interaction studies to optimize long-term patient outcomes.

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Conflict of interest

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Author contributions

The concept of this review (YID), search of literature, development of first draft (LWN, CID), editorial changes, and critical review of the manuscript (EDK, YID).

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