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Review Article

Genetics and therapeutic approaches for sickle cell disease

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Abstract

Sickle cell disease (SCD) is an inherited blood disorder characterized by hemolytic anemia, vaso-occlusive crises, relentless end-organ injury, and premature death. Currently, red blood cell transfusion and hydroxyurea are the major disease-modifying therapies available for SCD. Hematopoetic stem cell transplant is curative, but barriers to treatment are substantial and include a lack of suitable donors, immunologic transplant rejection, long-term adverse effects, prognostic uncertainty, and poor end-organ function, which is especially problematic for older patients. Gene therapy to correct the bs point mutation is under investigation as another curative modality. Deeper insights into the pathophysiology of SCD have led to the development of novel agents that target cellular adhesion, inflammation, oxidant injury, platelets and/or coagulation, vascular tone, and hemoglobin polymerization. These agents are in preclinical and clinical trials. One such agent, L-glutamine, decreases red blood cell oxidant injury and is recently US Food and Drug Administration approved to prevent acute pain episodes of SCD in patients 5 years of age or older affecting the shape and movement of red blood cells in blood vessels, causing various health issues. However, a bright ray of hope involving research into anti-sickling properties of medicinal plants has been rewarding. This alternative therapy using phyto-medicines has proven to not only reduce crisis but also reverse sickling (in vitro).The paper mainly looks into treatment approaches such as conventional treatment strategy and genetic therapies. Furthermore, the paper communicates a comprehensive demographical understanding of the SCD in India. Additionally, the paper discusses the growing interest in using medicinal plants and nutrition to manage SCD, highlighting the significant benefits of phyto-medicine and on-going future research for the advancement of therapeutic approaches of existing therapy for SCD.

Keywords: Sickle cell anaemia, Conventional treatment, Gene therapy, Herbal treatment, On-going future research.

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1. Introduction

Red blood cells (RBCs) are the main component affected by sickle cell disease, an inherited genetic illness. SCD is caused by a genetic mutation that leads to the substitution of an amino acid (valine for glutamic acid) within the β-globin chain of haemoglobin (Hb), resulting in the formation of sickle Hb (HbS). Deoxygenation of HbS leads to polymerization, resulting in the formation of rigid, sickle-shaped RBCs. These distorted RBCs can block capillaries and cause permanent damage to cell membranes, often leading to hemolysis. Normal haemoglobin-containing red blood cells are smooth, flexible, and disk-shaped; they resemble holeless doughnuts. They have no trouble passing through blood vessels. Sickle cell hemoglobin causes stiff, sticky cells. They take on the shape of a sickle or crescent, resembling the letter C, when they run out of oxygen as depicted in **Figure 1**. It is difficult for these cells to pass through blood vessels because they adhere to one another. The flow of healthy, normal blood that carries oxygen may be obstructed by this in small blood vessels. The blockage can cause pain. The average red blood cell has a 120-day lifespan. Sickle cells only survive for 10-20 days. Due to their stiffness and shape, sickle cells may be eliminated by the spleen.[1-3]

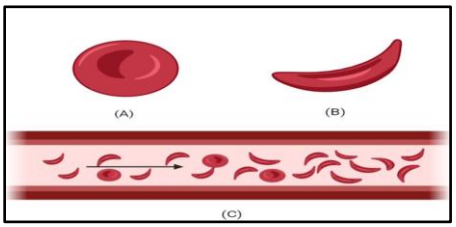

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Figure 1: (A) Normal Red Blood Cell, **(B)** Sickle Cell RBC, **(C)** Sickle cells blocking normal RBC flow.[81]

The presence of sickle shaped RBCs in human blood was first reported by Herrick (1910).[4] SCD affects a significant number of new-borns annually, with the highest prevalence found in regions such as sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries. Every year, the disease is transmitted almost 300,000 children Africa and WHO stated that nearly 80% of them die before the age of 5 years for lack of diagnosis and adequate care.[5]

It is estimated that around 50 million people in India carry the sickle cell trait, while approximately 1.5 million individuals have sickle cell. Many therapeutic approaches are proposed to relieve sickle cell disease patients from this painful and chronic disease, including - Bone marrow transplant, Blood transfusion, Crinalizumab, Gene therapy, Hydroxyurea, Hydroxycarbamide, L- glutamine, Voxelotor and herbal therapy.[6]

2. Demographical Status of Sickle Cell Disease in India

Sickle cell disease is a genetic blood disorder, and over 300,000 babies are born with every year[7] India is the second-highest country in the number of babies born with sickle cell disease,[8] between 2016 and 2018, a health screening in India, led by organizations like ICMR (Indian Council of Medical Research) found that out of 11,383,664 people checked, 47,311 had the disease, and 949,057 had the sickle cell trait.[9] India has a notable problem with hemoglobin disorders, like sickle cell disease, which affects different parts of the country.

In the Northeast, it's 0%–18%, in the West, 0%–33.5%, in the Central region, 22.5%–44.4%, and in the South, it's 1%–40%.[10] In simple terms, certain tribal groups in South Gujarat, such as Chaudry, Gamit, Rohit, Vasava, and Kukana, have a relatively high occurrence of two genetic conditions: HbS (6.3 to 22.7%), which is associated with sickle cell disease, and β-thalassemia trait (6.3 to 13.6%), which is a type of inherited blood disorder.[11.]

The Indian Red Cross Society, Gujarat State Branch, conducted extensive population surveys in which 1,68,498 tribals from 22 districts were screened. The findings revealed that the overall prevalence of sickle cell carriers among these tribal populations was 11.37%.[12]

Gujarat has 26 districts, with over half being tribal. It ranks as the 4th most populated state with scheduled tribes in India, following Madhya Pradesh, Maharashtra, and Orissa. Many people in Gujarat live in challenging terrains, particularly in the Eastern belt from Ambaji in the North to Dang in the South. This region encompasses districts like Dangs, Valsad, Navsari, Surat, and Bharuch in Southern Gujarat.[13]

The study took place in Korba district, Chhattisgarh, India, from June to October 2018. Korba was chosen because it has a significant number of marginalized communities (40.9% scheduled tribe, 10.33% scheduled caste) and is actively implementing strategies for Universal Health Coverage (UHC). All residents are covered by government-funded health insurance programs, ensuring access to a wide range of medical services. The district also has a certified district hospital and a well-established public health system with sufficient facilities.[14] Abnormal hemoglobin gene is the most common type of hemoglobinopathy globally, affecting a significant portion of the population.

As far as National prevalence of SCD is concerned, there is a lack of pan-India studies on the prevalence of SCD. However, scattered data is available and the state-wide sickle cell prevalence from published studies is shown in **(Table 1)** which also reflects the state-wide prevalence alongwith the web based survey data by ICMR.

Table 1: Prevalence of the sickle cell disease in Indian states[78]

States	Prevalence data from other studies [Numbers screened prevalence in %]	Prevalence data from ICMR study [Numbers screened prevalence in %] May2019- February 2023
Madhya Pradesh	505 (1.18%)	NIRTH-9,721 (0.69%)
Odisha	761 (1.7%)	RMRC—6,036 (1.57%)
Maharashtra	19,833,217 (0.08%)	NIIH and NIRRCH - 20,716 (0.48%)
Rajasthan	36,752 (0.17%)	NIIR-NCD—6,385 (0.54%)
Tamil Nadu	-	NAWA-2,170 (0.54%)
Chhattisgarh	38,472 (23%)	-
Gujarat	3,17,539 (0.31%)	SEWA Rural-8,117 (1.53)
	5,467 (0.60%)	
	8,411 (1.45%)	

3. Determinants of Disease Severity

Sickle cell disease (SCD) is the most prevalent monogenic disorder globally, attributed to the safeguard provided by heterozygosity against malaria.[15] While SCD predominantly affects sub-Saharan Africa, population migration and relocation have led to 1 in 2000 infants being born with SCD in the United States, and 1 in 67 infants will be carriers of heterozygosity.[16-18] Demographic trends and extensive enhancements in clinical care are expected to contribute to a rise in the percentage of the global population impacted by SCD. Most instances of SCD result from a homozygous variation in the HBB gene (p.Glu6Val), which encodes the β-

globin subunit of adult hemoglobin tetramer (α2β2). In low oxygen conditions within venous capillaries, sickle hemoglobin (α2βS2) forms inflexible polymers, leading to the rigidity, adhesiveness, and fragility of circulating red blood cells. This process initiates a multifaceted pathophysiology involving hemolysis, vascular occlusion, and inflammation as shown in **Figure 2**. This condition causes intense pain, weakens the immune system, harms multiple organs, and often leads to early death. The damage is linked to the breakdown of red blood cells, releasing harmful substances that contribute to various health issues like stroke, kidney problems, lung hypertension, priapism, and leg ulcers. Vessel blockages are believed to trigger sudden pain, chest problems, and tissue death,[19-78]

While SCD is a monogenic disorder, the symptoms vary among affected individuals. The impact of the environment on SCD is evident in the starkly different outcomes observed in sub-Saharan Africa, where around half of affected children succumb before reaching 5 years of age, compared to high-income countries where advanced medical support prolongs patient lifespan. Nevertheless, most patients in affluent nations still experience significant suffering and premature mortality.[20-21]

Manifestations of Sickle Cell Disease (SCD) are also impacted by genetic factors. For instance, remaining expression of fetal hemoglobin (HbF, α2γ2) in postnatal red blood cells, diminishing SCD severity by impeding sickle hemoglobin polymerization, is predominantly determined genetically. Co-inherited hereditary persistence of fetal hemoglobin, triggered by variations in the extended β-like globin locus, leads to exceptionally elevated levels of HbF, alleviating numerous symptoms of SCD.[22-23] Genome-wide association studies reveal that 20%-50% of the variability in HbF can be attributed to single-nucleotide variants (SNVs) in three loci: BCL11A, HBS1L-MYB, and the expanded β-like globin locus.[24-27]

The genetic factors influencing complications related to SCD are not well elucidated, despite the abundance of publications on this subject. For instance, a recent polygenic score that encompassed 21 single nucleotide variants (SNVs) across 9 genetic loci, including those influencing HbF, accounted for a mere 3.5% of the variability in acute pain episodes, serving as an illustrative example.[28]

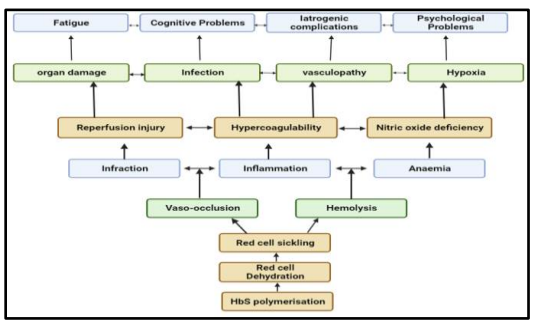

Figure 2: Determinants of severity in sickle cell disease[79]

4. Pathophysiology of Sickle Cell Anemia

Sickle cell anemia is an inherited disorder marked by a mutation in the β-globin chain, resulting in the substitution of valine for glutamic acid at the sixth position. This genetic change affects the β-globin gene on the short arm of chromosome,[11] leading to the synthesis of hemoglobin S (HbS) when two modified β-globin subunits combine. In low-oxygen conditions, HbS undergoes non-covalent polymerization, causing red blood cells to assume a sickle shape with reduced flexibility. The compromised elasticity is pivotal in sickle cell disease pathophysiology **(Figure 3)**, as sickle cells lack the adaptability of normal cells to navigate capillaries.[29-30]

Recurrent sickling episodes in low-oxygen environments result in cell membrane damage and decreased elasticity. Even with sufficient oxygen, the rigid cells struggle to regain their typical shape, leading to reduced deformability in narrow capillaries, ultimately causing vessel blockage and ischemia.[31-32]

Concerning anemia in sickle cell disease, hemolysis occurs, leading to the destruction of misshapen red cells in the spleen. Despite attempts by the bone marrow to produce new red cells, this proves inadequate to match the rate of destruction. While normal red blood cells typically live for 90-120 days, sickle cells exhibit significantly reduced survival, lasting only 10-20 days, as reported by ethno-medicine.

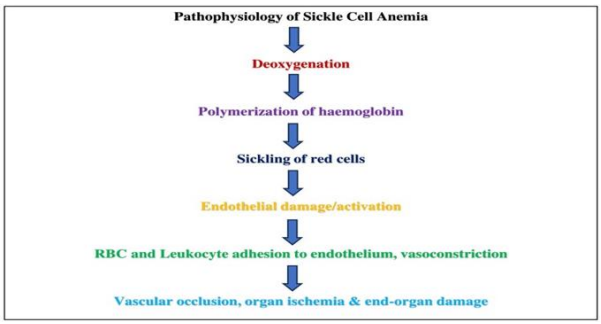

Figure 3: Schematic diagram of pathophysiology of SCD[82]

The SCD happens when valine takes the place of glutamic acid, the sixth amino acid, altering the structure and function of the protein **(Figure 4)**. On chromosome 11, a mutation is a single nucleotide substitution. Under low oxygen conditions, mutant hemoglobin polymerizes clumps together, and forms long rod bundles that bend red blood cells into the traditional sickle shape. Sickle cells have a sticky, stiff texture. They frequently obstruct the blood flow in the organs' and limbs' blood vessels and as a result may result in organ damage and pain.[33-34]

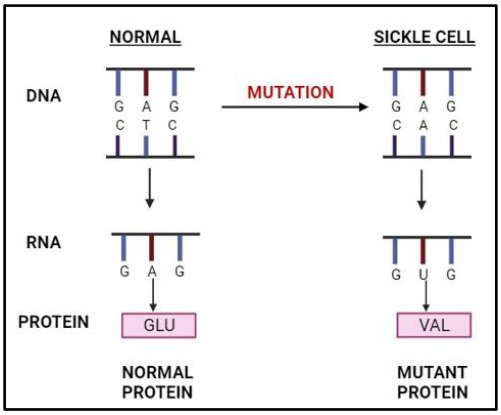

Figure 4: Effects at the DNA level**.**

4.1. Inheritance of sicklecelldisease

Sickle cell anemia is an autosomal recessive disease that occurs only when both the mother and father have missing copies of the HBB gene. In other words, if a person received her only copy of the defective HBB gene from her mother or father, she does not have sickle cell disease, but rather has the so-called "sickle cell trait." **(Figure 5)**. This means that someone has sickle cell anemia. People with anemia usually have no symptoms or problems, but they can pass the mutated gene on to their children. He says there are three genetic scenarios that can cause a child to develop sickle cell disease. Both parents suffer from sickle cell anemia. If both parents have sickle cell disease, there is a 25% risk that their child will develop sickle cell disease and a 50% risk that their child will develop sickle cell disease. He also has a 25% chance that his children will not inherit a copy of the mutated gene. One parent suffers from sickle cell anemia and the other parent also suffers from sickle cell anemia. If one parent has sickle cell disease and the other parent also has sickle cell disease, the child has a 50% risk of developing sickle cell disease; there are 50%.[35]

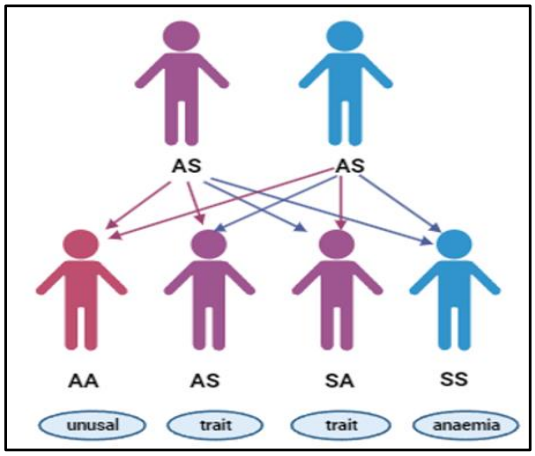

Figure 5: Pattern of inheritance of SCD[83]

5. Clinical Manifestation

Clinical manifestations of sickle cell disease can range from acute generalized pain to early onset stroke, leg ulcer and premature deaths from multi-organ failure.36 [36]. The effect of haemoglobin (HbF) delays the onset of clinical features until the middle to second part of the first year of post-natal life, at which point the haemoglobin has mostly switched to adult haeglobin.[37-40]

6. Approaches to the Sickle Cell Disease Therapy

Despite a clear knowledge of the disease's molecular nature, there is presently no recognized treatment for sickle cell anemia. There is a brief information about the development of treatment strategy has been represented in figure 6.

Finding substances that prevent or reduce the occurrence of hemoglobin polymerization crises in sickle cell disease has been approached in a number of ways-

Bone Marrow Transplantation In individuals with sickle cell disease, the bone marrow, responsible for blood production, generates red blood cells carrying hemoglobin S, contributing to the challenges associated with the condition. The objective of a transplant is to replace the cells producing hemoglobin S with those producing hemoglobin A. To prepare for the transplant, potent medications (chemotherapy) are administered to the patient to weaken or eliminate their own bone marrow cells, preventing rejection of the incoming donor blood cells. Subsequently, the patient receives bone marrow from a donor without sickle cell disease, possessing either normal hemoglobin or the sickle cell trait. The transplant is administered akin to a blood transfusion through an intravenous tube. The newly introduced bone marrow produces healthy red blood cells with lower levels of hemoglobin S, addressing the issues associated with sickle cell disease.[41-42]

6.1. Gene therapy

Gene therapy has the potential to provide more precise and efficient treatments, particularly for individuals with rare diseases where existing treatment choices are restricted.[43]

6.2. Casgevy

Casgevy is indicated for the treatment of SCD in patients at least 12 years of age with recurrent vaso-occlusive crises (VOCs). Targeted regions of DNA can be cut with CRISPR/Cas9, enabling precise editing (removal, insertion, or replacement of segments) where the DNA was cut. The patient is then given the modified blood stem cells back, where they attach and multiply in the bone marrow to increase the production of fetal hemoglobin (HbF), which helps carry oxygen to the cells and keeps red blood cells from sickling.[44]

6.3. Lyfgenia

Lyfgenia, which uses a lentiviral vector (gene delivery vehicle) for genetic modification, is indicated for the treatment of patients at least 12 years of age with SCD and a history of vaso-occlisove events (VOEs). Lyfgenia modifies

the patient's blood stem cells to produce HbAT87Q, hemoglobin derived with gene therapy that has a similar function to the normal adult hemoglobin produced in individuals without SCD, hemoglobin A. Further, red blood cells that have HbAT87Q have a lower risk of sickling and obstructing blood flow in patients.[45]

6.4. Genome editing

The introduction of specific reprogramming factors, circumventing the ethical issues surrounding embryonic stem cells, solid advances in genome editing with methods including zinc finger nucleases (ZFNs), transcription-activator–like effector nucleases (TALENs) and clustered regularly interspaced palindromic repeats (CRISPR)-associated protein-9 nuclease (Cas9) have brought the potential of introducing promising ideas to the clinic. These nucleases are proven to efficiently edit genomes of various animal models and human cells, and great efforts to bring these tools to the clinic have been pursued by academia and industry. These editing tools efficiently disrupt genes at defined lociand can also be used to promote homology directed repair (HDR) as a means of gene correction, although HDR is less efficient. Because β-globin disorders such as SCD are monogenic diseases, genome editing aiming to correct the mutated β-globin gene would be applicable to all affected patients, making this disorder an ideal target.[46-47].

7. Disease Modifier Agents

7.1. Hydroxyurea

Initially, hydroxyurea was used in clinical settings as a chemotherapeutic drug to treat leukemias and other solid cancers.48-49 [48-49]. For decades, the only treatment for sickle cell disease (SCD) approved by the U.S. Food and Drug Administration (FDA) was hydroxyurea, which was first licensed in 1998. It works by increasing the fraction of hemoglobin F and reducing the chance that cells may deoxygenate and polymerize.9[9] Beyond HbF induction, hydroxyurea's cytotoxic effects also lower platelet synthesis, reticulocyte, and neutrophil generation in the bone marrow—all crucial mediators of inflammation. Reducing WBC in SCA is potentially therapeutic in and of itself because increased WBC has been linked to both morbidity and mortality of SCA.[50-51] [Neutrophils and reticulocytes both use vascular adhesion to promote vaso-occlusion; hydroxyurea decreases both their absolute numbers and the surface expression of adhesion receptors.[52] Beneficial effects on the circulating red blood cells are among the other advantages of hydroxyurea therapy.

7.2. Voxelotor

Through a reversible binding process, it increases hemoglobin's affinity for oxygen, maintaining the oxygenated hemoglobin state and inhibiting HbS polymerization. These regions of Africa, the Middle East, and some regions of India are the most common places for this genetically inherited illness.Hb's affinity for oxygen is increased with voxelotor. The protein forms a covalent connection with the N-terminal valine of the α-chain, allowing for a reversible binding to hemoglobin (Hb) and causing an allosteric alteration of Hb[10-13] With a higher affinity for oxygen than hemoglobin, voxelotor maintains the oxygenated Hb state and inhibits HbS polymerization.[53]

7.3. L- glutamine

When L-glutamine was approved by the US Food and Drug Administration in 2017 as a therapy to reduce acute complications in patients with sickle cell disease (SCD), it was a welcome addition to the limited range of treatment options for this populations.[54] Sickle cell blockages can cause harm, but Lglutamine can lessen such damage. Those who take L-glutamine for sickleell disease may experience fewer hospitalizations and pain crises.

7.4. Crizanlizumab

It inhibits or prevents platelets, white blood cells, and red blood cells from adhering to the walls of blood vessels and to one another. An infusion is the sole monoclonal antibody authorized for use in the treatment of SCD patients is crizanlizumab.[55]

In sickle cell disease patients 16 years of age and older, it is recommended as a preventive measure against repeated vaso-occlusive crises (VOCs). It can be used as a monotherapy in patients for whom hydroxyurea is inappropriate or as an adjunct to hydroxyurea therapy.[56]

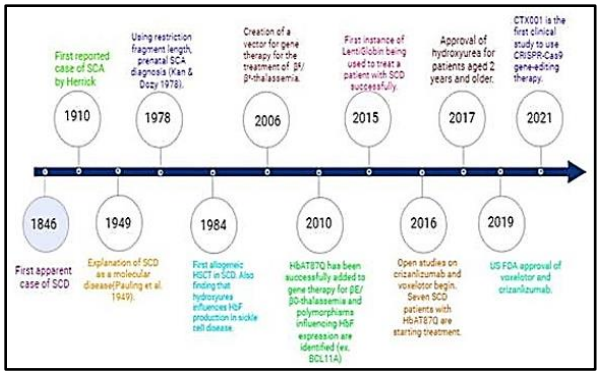

Figure 6: Chronology of significant discoveries and clinical progress on SCD.[84]

Apart from above mentioned clinical agents; recently approved medicines for SCD are collected in table **2**.

Table 2: Current approved pharmacological treatments for sickle cell disease.[57-59]

Medication	Year of FDA approval	Approved age group	Therapeutic Effects	Mechanism of action
Hydroxyurea	1998 in adults and 2017 in children	>9 months	Decreases intracellular HbS polymerization, Increases HbF production	Ribonucleoside diphosphate reductase inhibitor
L-Glutamine	2017	>5 years	Increases RBC reducing potential	Increases , nicotinamide adenine dinucleotide phosphate
Crizanlizumab	2019	>16 years	Decreases erythrocyte and leukocyte adhesion	Monoclonal antibody against P-selectin
Voxelotor	2019	>12 years	Decreases HbS polymerization & Delays production of deoxyhemoglobin	Increases Hb affinity for oxygen

Table 3: Medicinal plants found in Indian region for the management of SCD[69-72]

Sr. No.	Medicinal plants	Common name	Parts used	Main active constituents	nti –sickling Action
1.	Acacia catechu Wild Family Fabaceae.	Cutch tree,Kahir and Khadira	Leaf	4-hydroxybenzoic acid; kampferol; quercetin	Anti-platelet aggregatory, antioxidant and free radical scavenging.
2.	Allium sativum L Family Liliaceae.	Garlic	Rhizo me	Diallyl disulfide; flavonoids; carotenoids; ascorbic acid.	Antisickling suppress hemolysis and reduced membrane deformability
3.	Aloe barbadensis Mill. Family - Liliaceae	Aloe vera	Leaf	Barbaloin; steroids; acemanna; emodin.	Antisickling
4.	Cajanus cajan (L) Millsp Family Fabaceae	Adhaki, Arhar, Pigeon pea.	Seed	Phenylalanine; tyrosine; tryptophan; peptides; phydroxybenzoic acid; cajanin, concajanin, vitexin, isovitexin	Sickling reversal, inhibition of sickling, delayed gelation and increase oxygen affinity of HbS, membrane stability
5.	Carica papaya L. Family Caricaceae	Papaya, pawpaw	Unripe fruit	Tyrosine; phenylalanine; tryptophan; papain; organic acid released from fermentation	Antisickling and reversal of sickling
6.	Citrus sinensis L. Family Rutaceae	orange or sweet orange.	Fruit	Vitamin C; carotenoids	Antisickling
7.	Coleus kilimandschari Gurke Family Lamiaceae	Hedgehog flower, flybush, spurflower, and hullwort.	Leaf	Coleon U	Antisickling
8.	Cymbopogon citratus (DC ex Nees) Stapf. Family Poaceae	Lemon grass	Leaf	Essential oil (citral and terpenes)	Reversal of sickled erythrocytes
9.	Eugenia caryophyllata (L.) Family Myrtaceae	clove	Fruit, Leaf, stalk	Eugenol; eugenyl acetate; β-caryophyllene; gallotannic acid	Antisickling
10.	Mangifera indica Linn. Family Anacardiacea	mango, aam	Bark	Limonoid	Anti-anemic
11.	Vigna subterranean L. Verde. Family Fabaceae	Bambara groundnut	Seed	flavanols, anthocyanindins, isoflavones and phenolic acids.	Sickling inhibition, sickling reversal, and delay polymerization
12.	Vinca minor L. Family Apocynaceae	lesser periwinkle or dwarf periwinkle	Entire plant	Vincamine; cromesilic acid.	Sickling reversal, ant sickling

Table 4: Medicinal plants found in other region for the management of SCD[70-72]

Sr. No.	Medicinal plants	Common name	Parts used	Main active constituents	Anti-sickling action
1.	Adansonia digitata L. Family Bombacaceae.	baobab tree	Bark, fruit, leaf	gallic acid and epicatechin-(4β→8)-epicatechin (procyanidin B2).	Antisickling, boost red blood and white blood cell count.
2.	Cyperus esculentus L. Family Cyperaceae	yellow nutsedge or tiger nut, nut grass,	Seed	Arginine; lysine; serine.	Antisickling, Antigellation of sickled cells, improved oxidant status of erythrocytes
3.	Dennettia tripetala Family Annonaceae	Pepperfruit	Fruits, seeds	β-caryophyllene, myrcene, limonene	Prevent sickle hemoglobin polymerization by stabilizing the membrane of red blood cells.
4.	Lawsonia inermis L. FamilyLythraceae.	Henna	Leaf	2-hydroxy-1,4-napthaquinone; isoplumbagin	Antisickling, increase the oxygen affinity of HbSS blood
5.	Piper guineensis Schum. & Thonn Family Piperaceae	Ashanti pepper	Fruit	Piperine	Antisickling
6.	Pterocarpus osun Craib Family Papilionaceae.	Bloodwood	Stem	Tannins; saponins	Antisickling
7.	Senna alata L. Family Leguminosae	Andle bush, ringworm bush, craw-craw plant, andcapulo.	Leaf	Terpenes; sterols; Kaempferol; crysophanol.	Membrane stability
8.	Stephania cepharantha Hayata Family Menispermaceae.	Stephania corymbosa (Blume) Walp.	Leaf	Cepharantine	Sickling reversal, antisickling, delay gelation of HbS
9.	Sorghum bicolor L. Moench Family Poaceae.	Great Millet, Broom Millet & guinea corn	Leaf, seed	p-hydroxybenz-aldehyde; phenylalanine; tryptophan	Antisickling
10.	Zanthoxylum zanthoxyloides (Lam) Waterm Family Rutaceae	Senegal prickly-ash	Root, root bark	p-Hydroxybenzoic acid; zanthoxylol; divanilloyl quinic acid; pellitorine; fagaronine; 2- hyroxymethyl benzoic acid.	Antisickling, reversal of sickling

8. Herbal Drugs Used in the Management of SCD

Herbal therapy is a widely accepted practice for the treatment of SCD patients, particularly in the rural communities of West Africa where the disease is endemic. Active crude extracts (ACEs) from medicinal plants prepared according to traditional recipes are also used in the formulations of current indigenous drug development processes.[60]

For instance, the National Institute for Pharmaceutical Research and Development (NIPRD) created the herbal medication NIPRISAN^{TM,} which is extensively used in Nigeria, India, and the United States and has demonstrated encouraging signs of efficacy.[61-63]

It has been reported that the anti-sickling phytomedicine Nicosan (formerly called as Niprisan) inhibits hemoglobin S polymerization. it is a cocktail of four medicinal plants: Sorghum bicolor, Pterocapus osun, Eugenia caryophyllum, and Piper guineense. The potential could have arisen from the combined action of the individual herbs chemical constituents.Therefore, the combined antisickling, antipolymerization, antidehydration, and antioxidant effects from the component plants may account for the phytomedicines observed therapeutic effect, as is common with most herbal remedies. For the treatment of sickle cell disease (SCD), numerous herbal recipes and formulations made from medicinal plants have been documented by a number of writers and researchers.[64-66]

These therapeutic plants have demonstrated a variety of actions in the context of sickling-polymerization, antioxidants, anti-inflammatory, analgesic, anti-pyretic, anti-dehydrating, and anti-osmotic effects, among other effects

[67]. All of these effects work together to provide a more stable and bearable patient condition.

A herbal remedy called Ciklavit®, which is derived from plant extracts called Cajanus Cajan is used to treat sickle cell anemia. But in a randomised controlled trial, it was unable to demonstrate any benefit in lowering SCA crises [68]. Some plants that have been scientifically proven to be used in SCD ethnomedicine are in the following families: Acanthaceae, Anacardiaceae, Apocynaceae, Bombacaceae, Caricaceae, Combretaceae, Cyperaceae, Euphorbiaceae, Fabaceae, Geraniaceae, Lamiaceae, Liliaceae, Lauraceae, Lythraceae, Meliaceae, Menispermaceae, Myrtaceae, Papilionaceae, Piperaceae, Poaceae, Rutaceae, Sterculiaceae (**Table 3** & **Table 4**).[69-73]

This review includes information on about 12 plants found in Indian region **(Table 3)** and 10 plants found in other region for the management of sickle cell anemia **(Table 4)** that are members of the specified families. Numerous biological properties of some of these plants have been documented, such as antiviral, antifungal, antimalarial, antimicrobial, antidiabetic, anticancer, anti-inflammatory, anti-tumor, antiulcer, immunomodulatory, and antioxidant properties. Zanthoxylum zanthoxyloides (Lam.) Waterm has been shown to be highly effective in managing sickle cell disease (SCD) despite having a broad variety of biological activities.[74]

9. Future Research

Several therapeutic treatments for SCD are in different stages of clinical development,such as prasugrel and oral anti-coagulants. Curative approaches for treating SCD arealso emerging, including gene therapy.

9.1. Prasugrel

Prasugrel, an oral therapeutic that inhibits adenosine diphosphate (ADP)-mediatedplatelet activation and aggregation, has been investigated in clinical trials for reductions in vaso-occlusive pain. Early trials showed promising trends, with decreased plateletactivation and a reduction in vaso-occlusive pain observed. However, observationsfrom a multicenter multinational phase 3 clinical trial involving 341 children with SCD showed no significant decreases in vaso-occlusive pain events.[75]

9.2. Mitapivat

Mitapivat, an innovative oral compound and the first of its kind, acts as an activatorof erythrocyte pyruvate kinase (PKR). Originally explored in patients with pyruvate kinasedeficiency (PKD), Mitapivat exhibited noteworthy improvements in hemoglobin (Hb) concentrations for non-transfusion-dependent patients and alleviated transfusion burdensfor those undergoing regular transfusions. Its approval in 2022 for PKD treatmentmarked a significant milestone. Furthermore, Mitapivat's potential extends beyond PKD toencompass other hereditary chronic conditions linked to hemolytic mechanisms of anemia,including sickle cell disease (SCD) and thalassemia.In the context of SCD, Mitapivat has been shown to be effective in a number of clinicaltrials.[76]

In addition to traditional gene therapy approaches, recent breakthroughs in genetic engineering have introduced innovative methods for treating SCD. Notably, gene editing techniques such as base editing and prime editing have garnered significant attention for their potential to correct the underlying genetic defects responsible for SCD.

9.3. Base editing

Base editing represents a remarkable advancement that enables targeted modificationsof specific DNA sequences without introducing double-strand breaks. Throughadenine base editors, researchers have achieved significant success in converting disease causingalleles to non-pathogenic variants. Notably, these techniques have led to substantialimprovements in hemoglobin production and reduction in sickling-related complicationsin preclinical models. Base editing's precision and efficiency offer a promising alternativeto conventional gene therapy methods.A recent study demonstrated the feasibility of producing therapeutic levels of base edits in multi-lineage-repopulating and self-renewing human hematopoietic stem cells (HSCs). Base editing can potentially offer a high purity gene-corrected product compared to nuclease based editing.[75]

9.4. Prime editing

An alternative avenue emerges with gene correction through CRISPR/Cas9 nuclease,which induces double-strand DNA breaks at mutated alleles for homology-directedrepair. While addressing the disease-causing allele, CRISPR/Cas9 nuclease-based methodsmay raise HSC engraftment issues due to the DNA damage response elicited by bothCRISPR/Cas9 and adeno-associated virus vectors.To tackle these challenges, Li et al. introduce an innovative approach that couldrevolutionize gene therapy for SCD. This method employs prime editing, a precisestrategy that utilizes a catalytically impaired Cas9 nickase. Prime editing stands out byincorporating a reverse-transcribed RNA sequence within the target-specific prime editingguide RNA. This mechanism enables targeted DNA repair while significantly limiting thegeneration of unintended insertions and deletions at the target site, substantially enhancingsafety.[77,80]

10. Conclusion

There are many promising treatments for SCD that have been recentlyapproved or are in development. Conventional treatments, such as hydroxyurea, have been used for decades and are effective for treating SCD-related painful episodes. However, hydroxyurea can produce a range of side effects, and the precise mechanisms of action for hydroxyurea are still under investigation. In addition we have given the list of

herbal resources; which are playing key role in the management of SCD because negligible chances of toxic effect also minimizing the risk of associated complications. Recently the FDA-approved treatments, voxelotor, crizanlizumab, and L-glutamine, have also been proved effective for reducing the frequency and severity of vaso-occlusive crises and improving overall quality of life for SCD patients, providing additional treatment options for SCD. For curative treatments, stem cell transplantation remains the only curative treatment option available for SCD, but its use is limited by risks and challenges and is still in development. However, gene therapy has also shown promising results recently, and even though more studies and clinical trials are needed to investigate the efficacy and safety of this treatment option, this approach provides hope as a future curative treatment option.

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12. Conflict of Interest

None.

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