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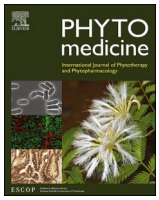

Review

Targeted therapeutic management based on phytoconstituents for sickle cell anemia focusing on molecular mechanisms: Current trends and future perspectives

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ABSTRACT

The global epidemic of Sickle cell anemia (SCA) is causing thousands of children to die. SCA, a genetic disorder affecting the hemoglobin-globin chain, affects millions globally. The primary physiological issue in these patients is the polymerization of sickle hemoglobin within their red blood cells (RBCs) during their deoxygenating state. The RBC undergoes a sickle shape due to the polymerization of mutant hemoglobin within it and membrane deformation during anoxic conditions. To prevent complications, it is essential to effectively stop the sickling of RBCs of the patients. Various medications have been studied for treating SCA patients, focusing on antisickling, γ-globulin induction, and antiplatelet action. Natural and synthetic anti-sickling agents can potentially reduce patient clinical morbidity. Numerous clinical trials focused on using natural remedies for the symptomatic therapy of SCA. Medicinal plants and phytochemical agents have antisickling properties. Recent studies on plant extracts' natural compounds have primarily focused on *in vitro* RBCs sickling studies, with limited data on *in vivo* studies. This review discussed the potential role of phytoconstituents in the management of SCA.

Introduction

Sickle cell disease (SCD) is a genetic blood disorder affecting around 100,000 individuals in the US (Snyder, 2022). SCD is a significant single-gene disorder affecting approximately 72,000 people in the US, with 2 million carriers. Over 200,000 infants are born annually in Africa with SCD (Jastaniah, 2011). A study of 128 sickle cell anemia (SCA) patients found 19 deaths, with septic shock and cardiogenic shock being the leading causes (Pompeo et al., 2022). SCD affects 300,000 infants annually globally, primarily in sub-Saharan Africa, India, the Mediterranean, and the Middle East, with around 100,000 in the US (Kavanagh et al., 2022). Africa faces an estimated 50-90% of SCA children dying before age 5, with an estimated 150,000-300,000 annual deaths, estimated for 5-10% of total child mortality (Diop and Pirenne, 2021). SCD affects approximately 14,000 people in the UK (Dormandy et al., 2018). The study involved 107 patients with a confirmed diagnosis of SCA, with 54.2% male and 45.8% female (Salih, 2019). A study in Kenya found that 3.1% of children aged 0-13 years had severe SCA, with 69.3% being previously undiagnosed. The incidence of all-cause hospital admission was higher in children with SCA than those without. The Kilifi Algorithm, based on five clinical features, could have identified approximately half of all SCA cases among hospital-admitted children (Macharia et al., 2018). SCD is a common cause of stroke in children and adults. Newborn screening, vaccination, and transcranial Doppler screening have reduced stroke incidence by up to in children (Kirkham and Lagunju, 2021). SCA is a global health concern, with India having the second-highest burden. A geodatabase of SCA surveys in India has generated the first India-specific map of sickle-cell allele frequency

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(Hockham et al., 2018). A total of 6,813 deaths caused by SCA were recorded. The majority of brown people (50.87%) were male, and 50.4% belonged to the age range of 25-34. The Midwest region experienced a higher mortality rate of 0.25 per 100,000 inhabitants (Mota et al., 2022). SCD is primarily caused by a single alteration in the gene that specifies the sickle-hemoglobin chain. The sickle erythrocyte is damaged when sickle hemoglobin (HbS) consists of polymers when deoxygenated. Due to a complex pathophysiology, SCD is characterized by erythrocyte damage, hypoxia, oxidative impairment, inflammation, abnormal intracellular links, and decreased nitric oxide bioavailability (Steinberg, 2008). SCD is a genetic hemolytic anemia characterized by the predominant presence of hemoglobin. The erythrocyte membrane is damaged, and the rapid intracellular polymers of HbS in anemic conditions significantly alter the shape and flexibility of the membrane. Rigid red blood cells (RBCs) cause hemolysis and hypoxia, while sickle-like erythrocytes accumulate and obstruct blood flow in thin arteries. Vaso-occlusion is a complex process involving long-term inflammation and abnormalities in vascular endothelium functioning. Homozygous HbS, also known as SCD, is a common and potentially dangerous form of SCD originating from both parents. SCA is characterized by severe clinical signs such as hemolytic anemia, splenic dysfunction, increased infection susceptibility, painful vaso-occlusive episodes, stroke, persistent organ failure, and increased mortality. Newborn hemoglobinopathy testing in the US and Europe has significantly reduced early mortality through essential vaccinations and early preventive treatments such as penicillin prophylaxis (Quinn et al., 2010; Telfer et al., 2007). However, early diagnostic capabilities are weak, and childhood mortality is high in many low-resource regions where the sickle cell load is largest (Grosse et al., 2011; McGann, 2014). HbS, rather than the usual hemoglobin (HbA) is produced due to the sickle mutation in the HBB gene that codes for globin. Scientific discovery of antisickling properties in medicinal plants such as *Parquetina nigrescens, Carica papaya* leaves, *Zanthoxyllum zanthoxyloides* root, *Cajanus cajan* seeds, and *Zanthoxyllum zanthoxyloides* root led to search for substitute, toxic-free, and less expensive therapies (Imaga et al., 2009; Mojisola et al., 2008; Oduola et al., 2006; Oduola et al., 2007a; Oduola et al., 2007b). The study explores the use of medicinal plants with antisickling properties in treating SCD and demonstrates various methods for evaluating the antisickling properties of herbal extracts. It also uses biochemical research to explain the antisickling effects that have been observed (Imaga, 2010). SCD is treated globally using plants, particularly in Africa and Asia. The study showed the medicinal benefits of treating SCA (Okpuzor et al., 2021). To select the most suitable articles for this study, a comprehensive search was conducted on significant medical, biological, and chemical databases such as Scopus, PubMed, and Web of Science. The search used the keywords "Sickle cell anemia, pathophysiology, and therapeutic strategies." In addition, the secondary keywords used were “Risk factors and diagnosis." We discussed the many benefits and treatment strategies of using plants and phytochemicals to treat SCA.

Epidemiology

SCD is a global RBC disorder affecting millions (Nurain and Bewaji, 2017). The disease is primarily distributed in sub-Saharan Africa, India, and the Caribbean, while interventions are mainly available in North America, Europe, and the Middle East (Piel et al., 2023). SCD is believed to have killed around 114,800 people globally who lived in tropical and subtropical sub-Saharan Africa (Adio et al., 2022). Between 2000 and 2018, Brazil reported a total of 9817 deaths related to SCD over 19 years (Santo, 2022). Over 300,000 children worldwide are born with SCD annually, with over 75% of cases occurring in sub-Saharan Africa (Esoh et al., 2021). Almost 80% of the 300,000 affected newborns born annually are estimated to be in Africa. Around 100,000 Americans, primarily African Americans, are affected by SCD (Hassell, 2010, 2016). From 1979 to 2017, 25,665 SCD-related deaths were reported in the US, with a decline in children and an increase in adults. Acute causes were more common in younger age groups, while chronic complications were more common in adults (Payne et al., 2020). SCD is the most prevalent severe monogenic disease, with a 50%-90% mortality rate in Africa before age five. SCD affects 1% of births in Africa, causing 6-15% of fatalities in children under 5, and is responsible for 6-15% of all deaths. Approximately 75% of people affected with SCD reside in sub-Saharan Africa, where an estimated 240,000 infants with HbSS are born annually (Uyoga et al., 2019). SCA is distributed in sub-Saharan Africa, the Middle East, and certain regions of India. SCA is the third leading cause of hospital admissions and mortality among children in Africa. SCA is a common disease in Saudi Arabia (Hazzazi et al., 2020). Many people with HbSC disease reside in West Africa (Kato et al., 2018). In the US, 30% of all SCD patients had HbSC diseases. HbSC disease can lead to severe health complications (Pecker et al., 2017).

Risk factors of sickle cell anemia

SCD can be classified into homozygous HbS and HbS/HbC co-inheritance, also known as HbSC. The condition is caused by a genetic mutation that disrupts the iron-rich molecule essential for blood redness and oxygen transport (Adio et al., 2022). Malaria is a significant cause of mortality in people with SCD (Eleonore et al., 2020). The study showed that certain clinical risk factors (Fig. 1), including the SEN-S globin gene haplotype, increased white blood cell count, seizures, and low painful episodes (Kinney et al., 1999).

Pathophysiology

Physiopathology of SCA. Hemolysis and Vaso-Occlusive Crisis, two main components of SCA, are present (Fig. 2).

The HbS mutation

The SCD is caused by a mutation in the gene encoding hemoglobin subunit β (HBB), resulting in various genotypic variants. This leads to diverse phenotypes and numerous complications, ranging from benign to fatal. The Hemoglobin SS (HBSS) genotype is a severe form of SCD, often associated with numerous complications (Khamees et al., 2021). HbS is a genetic variant of human hemoglobin caused by a point mutation in the β globin gene, resulting in the substitution of glutamic acid for valine (Mandal et al., 2020). The HbS mutation, which protects against malaria and is widespread in Africa, is in the HBB region of interest. This mutation is a significant example of adaptation through natural selection and random mutation (Melamed et al., 2022).

HbS polymerization

SCD is caused by the polymerization of HbS, which results in the sickling or destruction of RBCs (Brown et al., 2021). HbS polymerization leads to RBC sickling, chronic hemolysis, and vaso-occlusion (Brandow and Liem, 2022). GBT021601 effectively inhibits HbS polymerization and prevents RBC sickling (Dufu et al., 2020). The study reports preliminary safety, efficacy, and pharmacodynamic data from a phase 2/3 study of GBT021601 (NCT05431088) in patients with SCD (Saraf et al., 2023). The FDA has approved Voxelotor, a HbS polymerization inhibitor, for treating SCD (Han et al., 2020).

Diagnosis

Early detection of SCD can significantly decrease mortality rates and facilitate effective disease management. Various techniques have been developed to detect SCD and its carrier states with high sensitivity and specificity. The methods include screening tests such as complete blood count, peripheral blood smears, and sickling test. Confirmatory tests, such as hemoglobin separation techniques, are also utilized. Genetic

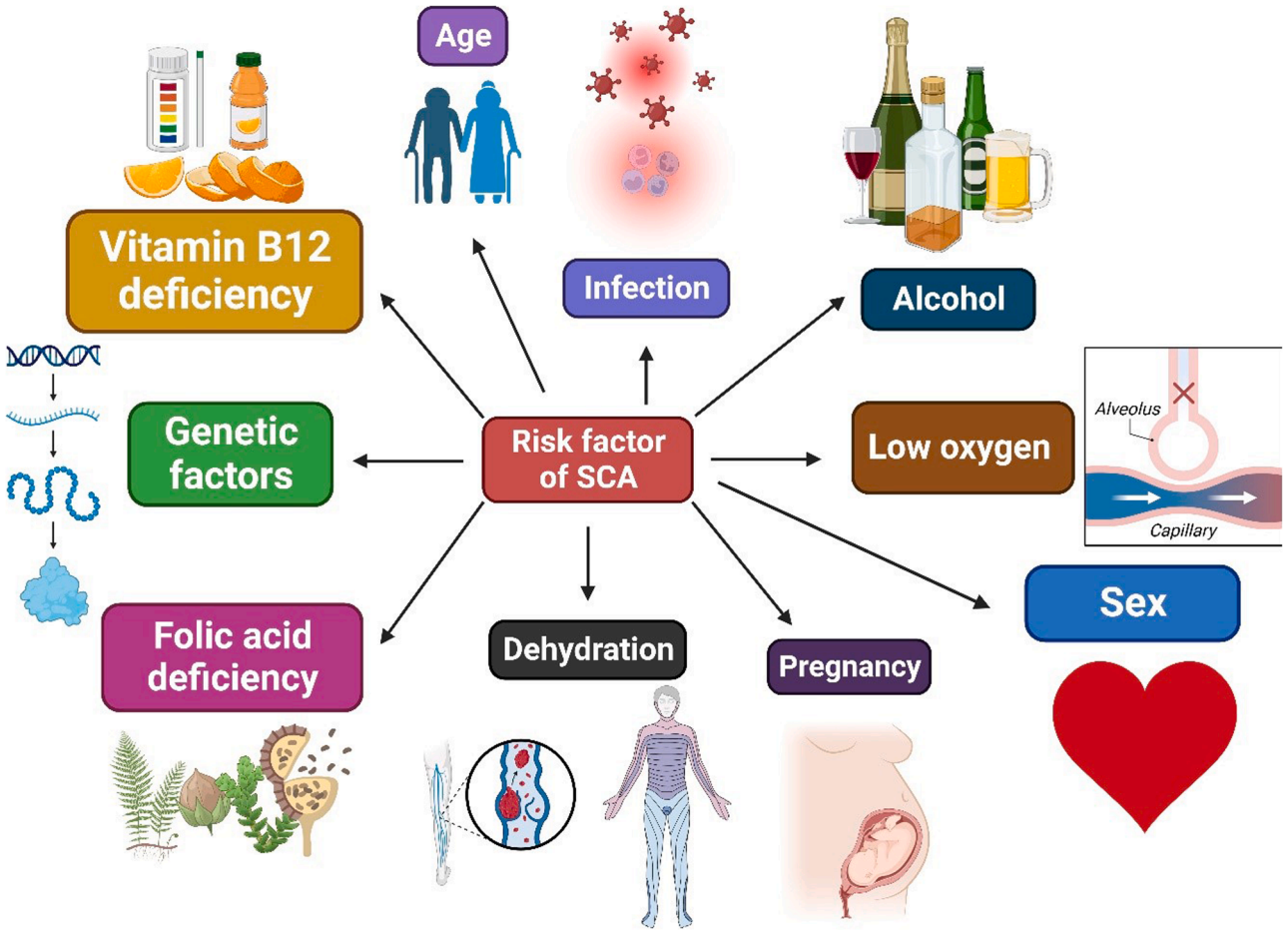

Fig. 1. Risk factors for sickle cell anemia. Several risk factors are responsible for developing sickle cell anemia, which is caused by a gene mutation that affects the production of hemoglobin, an iron-rich molecule in red blood cells.

tests are expensive and require skilled personnel in centralized labs (Arishi et al., 2021). The study investigates diagnostic methods such as genetic testing, hemoglobin electrophoresis, and advanced imaging methodologies, focusing on their accuracy and clinical applicability. Novel therapeutic approaches such as gene modification, fetal hemoglobin induction, and targeted therapies are being explored for their potential to improve SCA-related complications and patient outcomes (Buhari et al., 2023).

Plant extracts and phytochemical agents

SCD is a genetic disorder where an individual inherits the sickle cell allele from both parents. Modern disease-modifying therapies are expensive and often have side effects, prompting the search for natural alternatives from medicinal plants. The study aimed to assess the anti-sickling properties of medicinal plants (Sani et al., 2021). The anti-sickling potentials of hydroxyurea (HU), *Cajanus cajan* seed, and *Zanthoxylum zanthoxyloides* have been reported (Nurain and Bewaji, 2017). The study showed the use of *Z. zanthoxyloides* in managing SCA (Olushola-Siedoks et al., 2020). The study evaluated the antisickling properties of aqueous extracts of *Spirulina platensis* to enhance disease management (Teguem Tchoulegheu et al., 2023). Some plant-derived benzoic acid derivatives have anti-sickling properties (Pierre et al., 2015). *Rubia cordifolia* L. has anti-sickling properties (Mishra et al., 2021). *Azadirachta indica* J. seed oil has antisickling properties, which is used to manage SCD (Djote et al., 2020). The study showed the sickle-formation inhibition of a procedure containing *Z. leprieurii, Xylopia aethiopica*, and *Harungara madagascariensis*. Plant extracts exhibit potent antisickling properties due to their phytochemical constituents, including primary and secondary metabolites such as aromatic amino acids, alkaloids, phenolic compounds, saponosides, sterols, and polyterpenes (Joel et al., 2023). The study showed the efficacy of phytochemicals, specifically Rutin and its derivatives, for antisickling effects (Rathore et al., 2023). The study demonstrated using extracts from *Piper guineense, Pterocarpa osun, Eugenia caryophyllala*, and *Sorghum bicolor* phytochemicals for treating SCD (Mehanna, 2001). The phytochemical screening showed the presence of significant phytochemicals in all plant extracts, such as tannins, saponins, alkaloids, flavonoids, and glycosides. The study suggested that plant extracts can be a potential alternative treatment for SCD (Nurain et al., 2017). Furthermore, another study investigates the anti-sickling properties of Anogeissus leiocarpus, which is study investigates the anti-sickling properties of *Anogeissus leiocarpus*, used for managing SCD (Elufioye et al., 2020). The anti-sickling properties of *Buchholzia coriacea* and *Mucuna pruriens* seed extracts. Seed extracts have been identified as potential treatments for managing SCD (Ikechukwu et al., 2020). The study found that *Canna indica* and *Pergularia daemia* extracts have significantly more antisickling properties in *in vitro* studies compared to *Petiveria alliacea* (Iyekowa et al., 2023). Another study showed the *in vitro* anti-sickling activity and phytochemical analyses of the leaves of *Ocimum gratissimum*. It investigated ethyl acetate extracts, and their isolate have anti-sickling properties (Tshilanda et al., 2015). Extracts or compounds with radical solid scavenging activity also showed significant antisickling effects. The extract of *Mitracarpus villousus* contained quercetin, psychrorubrin, and a mixture of stigmasterol, each with varying activities (Elusiyan et al., 2018). Ajawaron HF has antisickling activities and is used to treat SCD

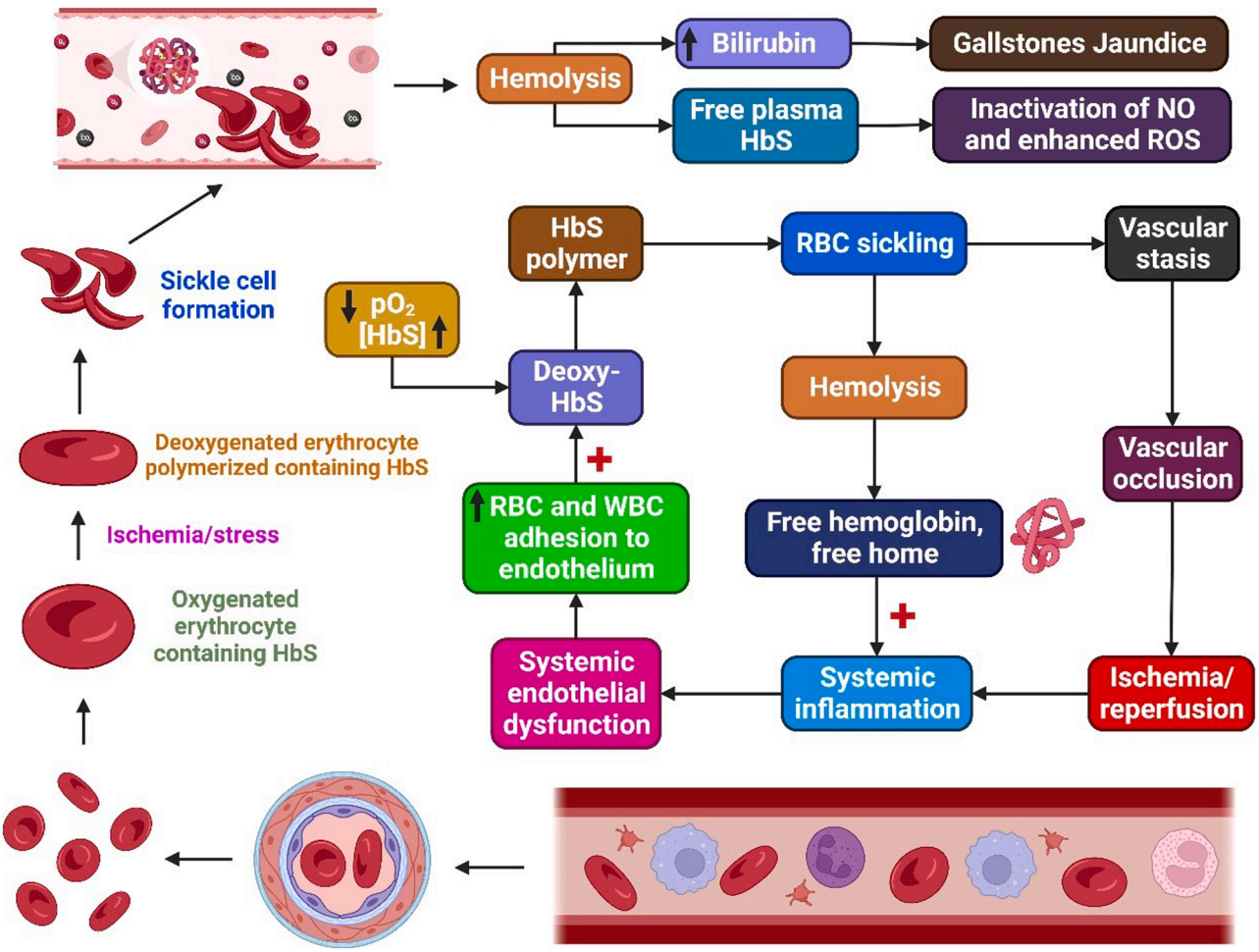

Fig. 2. Physiopathology of sickle cell anemia. Sickle cell disease is caused by mutation in the HBB, resulting in the production of HbS, which undergoes polymerization upon deoxygenation, damaging the erythrocyte and causing a diverse sickle cell population. Changes in body temperature, hemoglobin concentration, pH, and oxygen saturation levels can cause vaso-occlusion, hemolysis, and reduced endothelial nitric oxide. This can lead to nitric oxide deficiency, impaired blood vessel function, and increased arginase production.

(Imaga and Taiwo, 2017). Isomeric divanilloylquinic acids, isolated from *Fagara zanthoxyloides*, have been suggested beneficial in managing SCD (Ouattara et al., 2004). Natural products or phytoconstituents have antisickling activities to treat of SCA (Table 1).

New remedies for sickle cell anemia

Preventing polymerization

The polymerization of deoxy-HbS mainl causes the effects of SCA. The development of a drug that inhibits or reduces polymerization (Eaton and Bunn, 2017). Drugs are being tested for HbF, with new medications targeting chromatin regulators and DNA-binding transcription factors. BCL11A, a potent HbF repressor, plays essential roles in neural development and B cell function. Lineage-specific microRNAs in erythroid cells produce steady gene growth and increased HbF through short hairpin RNA-mediated inhibition of BCL11A (Brendel et al., 2016). Using genome modification technologies like zinc-finger nucleases or CRISPR/Cas9 may potentially damage the BCL11A erythroid-specific enhancer in intron 2 of the gene (Canver and Orkin, 2016; Vierstra et al., 2015). This chromosomal looping strategy enhances γ-globin expression while simultaneously decreasing it. Drugs are being developed to directly block polymerization and induce the synthesis of HbF (Eaton and Bunn, 2017). The natural aldehyde Aes-103 enhances the oxygen affinity of HbS by binding to the N-terminal valine residue of the γ-globin chain (Oder et al., 2016). Aes-103 was found to be well-tolerated, safe, and effective in inhibiting polymerization *in vitro* during an adult phase 1 dose-escalation trial (Oder et al., 2016). Although the entire analysis remains incomplete, preliminary outcomes of a phase 2 trial (NCT01987908) indicate no actual advantage of Aes-103 over a placebo. The study aimed to assess dose and safety, but further research is needed to determine the effectiveness of the potent treatment. A new medication has been developed using the same procedure but with greater precision and smaller doses (Ferrone, 2016; Metcalf et al., 2017). Initial phase studies confirmed the safety of polyaromatic aldehyde GBT440, indicating a dose-sensitive increase in hemoglobin, reticulocytes, sickled cells, and serum bilirubin levels, indicating less early hemolysis. The results of the multicenter phase 3 clinical studies of GBT440 on both adults (NCT03036813) and young children (NCT02850406) are eagerly estimated. Two promising methods for preventing sickling failed in clinical testing. Senicapoc (ICA-17043) targets the Gardos channel to combat dehydration and potassium release in SCA's intracellular pathophysiology. Phase 3 research was unable to prevent vasoocclusive diseases, despite initial signs of decreased hemolysis and improved erythrocyte survival (Ataga et al., 2011; Ataga et al., 2008). Sanguinate, a bovine PEGylated hemoglobin product, was developed to prevent HbS polymerization by providing potent antisickling chemical carbon monoxide. The phase 1 experiment (NCT02411708) was considered safe for a phase 2 trial (Misra et al., 2017). HbS polymerization is believed to play a significant

Table 1
This explores various natural products or phytoconstituents for their potential benefits in managing symptoms or complications associated with the condition of sickle cell anemia.

Natural products/ phytoconstituents	Study type	Mechanism of action	Major finding	Ref.
Omega-3 Fatty Acids	*In vivo*	The ω-3 fatty acid reduces liver injury in sickle cell mice by down-regulating HO-1 mRNA, decreasing HSP27 expression, and reducing dense red cell formation, demonstrating its multimodal action.	This affects the anti-oxidant systems, inflammation, and vascular activation in sickle cell mice, which suggests that it might be possible to treat SCD by improving vascular dysfunction.	(Kalish et al., 2015)
L-Arginine	Randomized double-blind	SCA is characterized by HbS development, intravascular hemolysis, and NO degradation. Supplementing with L-arginine aims to increase NO synthesis, acting as a vasodilator.	The study revealed that L-arginine supplementation, when combined with HU, increased nitrite and nitrate levels in SCA patients, which are markers of NO synthesis.	(Eleutério et al., 2019)
Vitamin E	*In vivo*	The presence of non-transferrin-bound iron (NTBI) in SCD may cause oxidative damage, potentially impaired by low levels of vitamin E. Vitamin E is an essential antioxidant that protects cells from the harmful effects of OS.	The study showed that patients with SCD have lower levels of vitamin E and higher levels of NTBI compared to controls. The study indicates a possible correlation between NTBI and vitamin E levels, indicating an inverse correlation.	(Marwah et al., 2001)
Curcumin	*In vivo*	Curcumin is antioxidant with anti-inflammatory properties, reducing OS and spinal neuroinflammation, and decreasing inflammation and OS in SCA patients.	Curcumin showed potential to reduce inflammation, OS, and hyperalgesia in sickle mice's spinal cords, suggesting they may recover chronic pain in SCA.	(Valverde et al., 2016)
Quercetin	*In vivo*	The therapeutic benefits of Quercetin were evaluated in mice. It has anti-adhesive properties, which help prevent vaso-occlusion.	Quercetin improves hypoxia-reoxygenation in mice, but reduces therapeutic benefits in control mice, suggesting HbS role in vaso-occlusion. Combining RBCs with antiadhesive therapies could be a novel treatment approach.	(Thangaswamy et al., 2021)
Black Seed	*In vitro*	It is known to have calcium antagonist and antioxidant properties, which are essential in managing SCA.	The study demonstrated in-vitro anti-sickling activity on 75% of patients with SCA, suggesting its potential for treatment.	(Dafaalla and Humeida, 2021)
Epigallocatechin gallate	*In vitro*	The substance may inhibit the transport of anion in RBCs, potentially reducing sickle cell dehydration caused by K-Cl cotransport or red cell storage.	It effectively prevents dehydration of sickle RBCs due to K-Cl cotransport or red cell storage. The substance inhibits K-Cl cotransport dehydration, increasing its inhibitory activity with hydroxyl group number, possibly through anion transport inhibition.	(Ohnishi et al., 2001)
Hydroxyurea	Randomized, double-blind, placebo-controlled	HU enhances fetal hemoglobin (HbF) levels and reduces vaso-occlusive complications in patients with SCA.	The study found that patients with higher HbF levels and fewer vaso-occlusive events had lower mortality rates. HU use reduced mortality in patients with frequent painful sickle cell episodes.	(Steinberg et al., 2003)
Flavonoids	*In vivo*	Flavonoids exhibit antioxidant activity, as their pre-incubation with RBCs significantly reduced the production of ROS induced by tert-butylhydroperoxide.	Flavonoids demonstrated superior antioxidant properties against excess ROS damage in SCA patients, suggesting an additional protective effect when combined with HU treatment.	(Henneberg et al., 2013)

role in the molecular etiology of acute and chronic SCD symptoms. Research has primarily focused on developing small antisickling molecules that can enter RBCs and directly prevent polymerization (Belhassen et al., 2001).

Vasoocclusion prevention and update

The vaso-occlusive process is indirectly impacted by the medications HU and decitabine (Teixeira et al., 2003). Research indicates potential in drugs targeting vas occlusion, with selectins developed as specialized inhibitors targeting endothelial adhesion substances. *In vitro*, studies have demonstrated the effectiveness of crizanlizumab, a systemically injected monoclonal antibody that attacks P-selectin, in blocking and reversing the sequestration process. Early outcomes of human trials have also proven promising. Recent research shows that people receiving high-dose crizanlizumab (5.0 mg/kg), taken systematically 14 times through the course of 52 weeks, had a 45.3% decreased rate of disease (Ataga et al., 2017). Increased Hb F levels inhibit Hb S polymerization, reducing intravascular hemolysis and erythrocyte sickling, thus reducing endothelial activation and NO consumption in blood vessels (Stuart and Nagel, 2004). The US FDA approved HU as the first medication to treat SCD, which is believed to work by inhibiting the enzyme ribonucleotide reductase (Fathallah and Atweh, 2006).

Correlation between hemoglobin structure and drugs

Boosting HbS's oxygen sensitivity can reduce the intracellular sickling process, which is a primary pathophysiology of SCD (Safo et al., 2011; Safo and Bruno, 2011; Safo and Kato, 2014). Hemoglobins exist in two quaternary states: T-state and R-state. T-state hemoglobin S displays sickling due to polymerization. A strategy is essential to prevent sickling or return to R-state (Safo et al., 2004), and it was shown that both HbA and HbS include allosteric sites where specific ligands are involved. Aromatic aldehydes have therapeutic effects by maintaining the relaxed R2-state of hemoglobin and increasing oxygen attraction through Schiff-base contact with N-terminal Val1 nitrogen and inter-subunit interactions (Safo et al., 2011; Safo and Bruno, 2011; Safo and Kato, 2014).

Physical pain and the biochemical basis of its relief

Pain is produced when painful stimuli activate a subset of sensory neurons' peripheral terminals through chemical, mechanical, or thermal means (Dellemijn and Fields, 1994). Acute pain and chronic pain have been identified as two different forms of pain in SCD. Vasoocclusion is related to acute pain. RBCs become less soft when HbS polymerizes into hard filaments under low oxygen pressure. Vasoocclusive crisis (VOC), acute pain that occurs in episodic, repeated, and unpredictable ways, is caused by such stiff RBCs that obstruct microcirculation (Ballas, 2015; Ballas et al., 2012; Rees et al., 2010). Physical pain is a sensation resulting from actual or potential tissue injury. Organisms have endogenous pain-controlling mechanisms due to the tendency of pain to persist beyond its expected duration. Ion channels and receptors interact to control such systems (Ameh et al., 2012). The distal tissue's

oxygenation is compromised and sustains ischemic-reperfusion injury during VOC. Acute pain is produced by this injury as a result of endothelial dysfunction, OS, and inflammation (Aich et al., 2016; Ballas et al., 2012). Pain that persists longer than three months is considered chronic (Yawn et al., 2014). With advancing years, most SCD patients experience persistent pain (Abdul Karim and Saaban, 2017; Smith et al., 2009).

Vanilloid and capsaicin receptor (TRPV1)

A characteristic of nociceptors is their sensitivity to capsaicin. Exposure to capsaicin stimulates nociceptor terminals in mammals, causing neuron activation, pain sensation, and local production of inflammatory mediators. Nociceptor terminals lose their sensitivity to capsaicin and other unpleasant stimuli after extended exposure (Jancso et al., 1977; Szolcsányi, 1993). Six subfamilies, referred to as TRPV1 to TRPV6, make up the known transient receptor potential vanilloid (TRPV) various channels (Camerino et al., 2007; Nilius et al., 2008; Szallasi et al., 2007; Venkatachalam and Montell, 2007). TRPVs are described as molecular thermometers because of their temperature sensitivity (Caterina et al., 1997). At 43 degrees Celsius, an acidic pH, allicin from garlic, vanilloids (such as piperine and capsaicin), and endocannabinoids all activate TRPV1. Capsaicin binds to TRPV1 on the membrane irritates or sensitive to heat neurons with a preference, which shows the ways sensitive to heat neurons with a preference, showing how the vanilloids work (Caterina et al., 1997). The average temperature range in which TRPV1 opens is 37 to 45 °C. Capsaicin increases heat by triggering the opening of the TRPV1 channel below body temperature. Capsaicin activates neurons, leading to the depletion of the presynaptic substance. Capsaicin does not affect neurons lacking in TRPV1 (Caterina et al., 1997; Szallasi et al., 2007).

Ion channels

Ion channels are lipid bilayer-spanning, macromolecular protein channels found in cell membranes. The energy required to maintain the concentration of sodium and potassium ions across the cell membrane is approximately 30% of the energy cells use. Ion channels utilize stored energy (Ackerman and Clapham, 1997). Ion channels are porous molecules that permit the transfer of ions (Ameh et al., 2012). The 28 members of the distinct class of transient receptor potential (or TRP) channels have various activation methods. Many are activated by their voltage, ligands, pH level, redox state, osmosis, temperatures, or physical stress, while some are naturally open (Camerino et al., 2007). They are more effective than enzymes because they can open a single channel from closed to open with a minor conformational change, allowing up to 10 million ions into or exit the cell per second. Most ion channels are classified based on the type of ion they permit, such as sodium, potassium, calcium, or chloride. They could be controlled by intracellular second messengers, transmembrane voltage variations, or external ligands (Ackerman and Clapham, 1997).

Medicinal plants

Cajanus cajan

Traditional Chinese medicine recommends *C. cajan* as a sedative and for the alleviation of pain (Ahsan and Islam, 2009). Nigerian natural treatment for SCD contains Cajan seeds' aqueous methanolic extract for strong antisickling efficacy (Ogoda Onah et al., 2002); The amino acids (phenylalanine is the most sensitive), phenolic compounds (p-hydroxybenzoic acid), tannins, globulins, and saponins. This has been proven to be effective and generally secure in preventing SCD. It has also been investigated as a potential treatment for aphtha, bedsore, and wound healing. Two globulins, cajanin and concajanin, have been identified by chemical tests (Pal et al., 2011). This substance has been extensively utilized to treat various diseases such as diabetes, ulcers, skin irritations, hepatitis, measles, jaundice, and dysentery. It can also remove bladder stones and regulate menstruation (Zu et al., 2010).

Cyperus esculentus

Cyperus esculentus is naturally found in warm temperate to subtropical areas (Zhang et al., 2022). The plant is commonly grown for its edible roots, known as tigernuts. Both people with SCD and healthy people in Southern Nigeria commonly ingest these seeds. There are unrecorded and unconfirmed reports of health benefits in SCD people who routinely consume these seeds. Preparations of methanol and aqueous extracts from the plant were utilized for the anti-sickling experiment. The gelation experiment showed that methanol and aqueous extracts of *Cyperus esculentus* have anti-sickling properties, with methanol extract showing a more prominent anti-HbS gelation effect (Nwaoguikpe, 2010).

Hymenocardia acida

Hymenocardia acida is a little plant (Danladi et al., 2021). This plant is frequently used alone or in combination with other botanical components to manage SCD. The phytochemical screening detected the existence of carbohydrates, tannins, flavonoids, saponins, alkaloids, cardiac glycosides, resins, steroids, and terpenes in the leaves of this plant. The ethanol extracts derived from the leaves have demonstrated the ability to reverse the sickling of human RBCs. Furthermore, it has been determined that this effect depends on the dosage administered. Studies have shown that saponins exhibit anti-sickling properties. The RBCs were observed to change from a sickle to a regular biconcave shape, and their size increased after 30 minutes (Ibrahim et al., 2007).

Alchornea cordifolia

Alchornea cordifolia is a small tree across tropical Africa (Boniface et al., 2016). The anti-sickling activity of the ethanolic and aqueous extract of the leaves of this plant has been assessed using *in vitro* methods. The aqueous extract exhibited superior anti-sickling action. The fractions underwent filtration, and the solvent was subjected to evaporation. The blood sample was introduced into the plant extract at varying quantities, utilizing a physiologic solution as the dilution solvent. Applying *Alchornea cordifolia* extract to sickle blood samples resulted in the normalization of erythrocytes, demonstrating the extract's impact on the sickling process of cells. The degree of normalization increases as the concentration of the extract increases. The study determined that the aqueous extract of *Alchornea cordifolia* has an anti-sickling effect (Mpiana et al., 2007).

Khaya senegalensis

Khaya senegalensis is before and after de-oxygenation African mahogany (Santos et al., 2022). The bark is frequently collected for use as a folk remedy. The stem, bark, and leaves of *Khaya senegalensis*, when extracted in water, showed a potent anti-sickling effect. The bioassay relied on quantifying sickle cells, both before and after de-oxygenation, in blood samples obtained from individuals suffering from severe SCA. These samples were pre-treated with the medications under investigation. The primary active component was limonoid. This limonoid demonstrated significantly greater anti-sickling activity *in vitro* compared to pentoxifylline, regardless of concentration and incubation conditions (Fall et al., 1999).

Parquetina nigrescens

Parquetina nigrescens has been proven as a natural botanical treatment for managing SCD (Adase et al., 2022). The study investigated the anti-sickling properties of leaves and stems, their impact on stabilizing erythrocyte membranes, and potential harm to organs. The freeze-dried

extract was utilized for anti-sickling investigations, osmotic fragility tests, and toxicological assessment. The osmotic fragility test revealed that various concentrations of *Parquetina nigrescens* plant extracts significantly protected RBC membranes. The herb also showed an inhibitory activity in the hemolysis of RBCs (Imaga et al., 2010).

Carica papaya

Carica papaya is indigenous to the tropical regions of the Americas and was initially cultivated in Mexico (Hernández-Salinas et al., 2022). The fermented blend of dehydrated immature fruit pulp from *Carica papaya* and dried leaves from *S. bicolor* exhibited anti-sickling characteristics. Both substances were combined in equal amounts in distilled water at the standard temperature of the room, and the experiment was conducted using sodium metabisulphite-treated sickled RBCs. The aqueous extracts were collected and utilized for anti-sickling experiments. The extracts were cultured for five days, and the extract obtained on the fifth day exhibited the most potent anti-sickling effects, with inhibitory activity of 93% and reversal activity of 84%. The anti-sickling capabilities of *Carica papaya* fruit pulp were evaluated in distilled water, methanol, and chloroform using sickled RBCs treated with sodium metabisulfite. The 5-day fermentation products demonstrated the most potent anti-sickling properties, with inhibitory activity of 87% and reversal activity of 74% when used at an optimal dose of 2.5 mg/ml. The methanol extract had a 64% inhibitory effect and a 55% reversal effect, whereas the chloroform extract showed no activity. The unripe fruit of *Carica papaya* contains the amino acids phenylalanine, tyrosine, and glycine, which have been identified as potential anti-sickling components and are responsible for the fruit's anti-sickling activity (Mojisola et al., 2009).

Toxicological evaluation

Scoparia dulcis is used in Africa as a treatment for SCD. This study aimed to investigate the plant's leaves' activity to prevent RBC sickling and its toxicological characteristics. The oral administration of the extract in mice resulted in an LD 50 value above 8000 mg/kg body weight. At 250 and 500 mg/kg doses, toxicological evaluations revealed minor congestion in nearly all the specified organs (Abere et al., 2015). The study investigates how *Cnidiscolus aconitifolius*' ethanol extract prevents RBC sickling in Wistar rats and evaluates its histological effects on the liver, kidney, and spleen. The LD50 of *Cnidiscolus aconitifolius* was assessed for its immediate and sub-acute toxicity in Wistar rats over 28 days at doses of 125, 250, and 500 mg/kg body weight. On the 29th day, rats were anesthetized and blood was obtained via heart wound for hematological evaluation. The rats' liver, kidney, and spleen were collected for histological evaluations (Cyril-Olutayo et al., 2020). The study evaluates the efficacy of Drepanoalpha®, an indigenous nutritional formula, in preventing RBC sickling, reducing harmful radicals, and assess its acute toxicity. Drépanoalpha®, as indicated by the biochemical and hematological markers in treated rats, appears safe due to its non-harmful effects on immune cells and blood clotting factors. The poly-herbal formulation improves hemoglobin levels in rats from 500 to 4000 mg/kg while preserving liver cell structural integrity. Drepanoalpha® can increase body weight and stimulate RBC and platelet production in people with SCD. This herbal remedy can potentially manage various types of anemia and potentially prevent bile duct obstruction or intrahepatic cholestasis (Ngbolua et al., 2014).

Conclusion and Future Perspectives

The study suggests that targeted therapeutic management of SCA using phytoconstituents has significant potential in reducing its pathophysiological manifestations. Researchers have discovered numerous potential therapeutic targets by the molecular mechanisms of phytoconstituents. Further research is needed to understand phytoconstituents' molecular mechanisms and the therapeutic effects. Developing innovative drug delivery systems could improve the bioavailability and targeted delivery of phytoconstituents, thus enhancing their therapeutic potential. Large-scale clinical trials are essential for confirming the safety and effectiveness of phytoconstituent-based therapies in diverse patient populations. We discussed the advantages and therapeutic approaches of using plants and phytochemicals to treat SCA.

CRediT authorship contribution statement

Md. Rezaul Islam: Writing – original draft, Investigation, Conceptualization. **Abdur Rauf:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Shopnil Akash:** Methodology, Investigation. **Muntasir Sharker:** Investigation, Methodology. **Mashiat Mahreen:** Investigation, Methodology. **Most Ayesha Khatun Munira:** . **Puja Sutro Dhar:** Methodology, Investigation. **Hassan A. Hemeg:** Investigation, Methodology. **Marcello Iriti:** Methodology, Supervision, Writing – review & editing. **Muhammad Imran:** Conceptualization, Investigation, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abdul Karim, S.A., Saaban, A., 2017. Shape preserving interpolation using rational cubic ball function and its application in image interpolation. Math. Probl. Eng. 2017.
Abere, T.A., Okoye, C.J., Agoreyo, F.O., Eze, G.I., Jesuorobo, R.I., Egharevba, C.O., Aimator, P.O., 2015. Antisickling and toxicological evaluation of the leaves of Scoparia dulcis Linn (Scrophulariaceae). BMC. Complement. Altern. Med. 15, 1–7.
Ackerman, M.J., Clapham, D.E., 1997. Ion channels—basic science and clinical disease. New Engl. J. Med. 336, 1575–1586.
Adase, E., Ankutse, P., Kumadoh, D., Archer, M.-A., Kyene, M.O., Yeboah, G.N., Asamoah Agyare, D.O., 2022. A review of Parquetina nigrescens (Afzel.) bullock, a plant for traditional medicine: phytochemical and pharmacological properties. Evid.-Based Compl. Altern. Med. 2022.
Adio, W.S., Christopher, F.C., Adesola, R.O., Mary, F.I., 2022. Current trends in the treatment of sickle cell anemia. World News Nat. Sci. 43, 60–75.
Ahsan, R., Islam, M., 2009. In vitro antibacterial screening and toxicological study of some useful plants (Cajanus cajan). Euro J. Sci. Res. 41, 227–232.
Aich, A., Beitz, A.J., Gupta, K., 2016. Mechanisms of pain in sickle cell disease. Sickle Cell Dis. 69–91.
Ameh, S.J., Tarfa, F.D., Ebeshi, B.U., 2012. Traditional herbal management of sickle cell anemia: lessons from Nigeria. Anemia 2012.
Arishi, W.A., Alhadrami, H.A., Zourob, M., 2021. Techniques for the detection of sickle cell disease: a review. Micromachines. (Basel) 12, 519.
Ataga, K.I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrisch, J., Guthrie, T.H., Knight-Madden, J., Alvarez, O.A., Gordeuk, V.R., 2017. Crizanlizumab for the prevention of pain crises in sickle cell disease. New Engl. J. Med. 376, 429–439.
Ataga, K.I., Reid, M., Ballas, S.K., Yasin, Z., Bigelow, C., James, L.S., Smith, W.R., Galacteros, F., Kutlar, A., Hull, J.H., 2011. Improvements in haemolysis and indicators of erythrocyte survival do not correlate with acute vaso-occlusive crises in patients with sickle cell disease: a phase III randomized, placebo-controlled, double-blind study of the Gardos channel blocker senicapoc (ICA-17043). Br. J. Haematol. 153, 92–104.
Ataga, K.I., Smith, W.R., De Castro, L.M., Swerdlow, P., Saunthararajah, Y., Castro, O., Vichinsky, E., Kutlar, A., Orringer, E.P., Rigdon, G.C., 2008. Efficacy and safety of the Gardos channel blocker, senicapoc (ICA-17043), in patients with sickle cell anemia. Blood J. Am. Soc. Hematol. 111, 3991–3997.
Ballas, S.K., 2015. Sickle cell pain. Lippincott Williams & Wilkins.
Ballas, S.K., Gupta, K., Adams-Graves, P., 2012. Sickle cell pain: a critical reappraisal. Blood J. Am. Soc. Hematol. 120, 3647–3656.
Belhassen, L., Pelle, G., Sediame, S., Bachir, D., Carville, C., Bucherer, C., Lacombe, C., Galacteros, F., Adnot, S., 2001. Endothelial dysfunction in patients with sickle cell

disease is related to selective impairment of shear stress–mediated vasodilation. Blood J. Am. Soc. Hematol. 97, 1584–1589.
Boniface, P.K., Ferreira, S.B., Kaiser, C.R., 2016. Recent trends in phytochemistry, ethnobotany and pharmacological significance of Alchornea cordifolia (Schumach. & Thonn.) Muell. Arg. J. Ethnopharmacol. 191, 216–244.
Brandow, A., Liem, R., 2022. Advances in the diagnosis and treatment of sickle cell disease. J. Hematol. Oncol. 15, 20.
Brendel, C., Guda, S., Renella, R., Bauer, D.E., Canver, M.C., Kim, Y.-J., Heeney, M.M., Klatt, D., Fogel, J., Milsom, M.D., 2016. Lineage-specific BCL11A knockdown circumvents toxicities and reverses sickle phenotype. J. Clin. Invest. 126, 3868–3878.
Brown, R.C.C., Redfern, A., Lisbon, E., Washington, C., Agodoa, I., Smith-Whitley, K., 2021. GBT021601, a next generation HbS polymerization inhibitor: results of safety, tolerability, pharmacokinetics and pharmacodynamics in adults living with sickle cell disease and healthy volunteers. Blood 138, 3099.
Buhari, H.A., Ahmad, A.S.a., Obeagu, E.I., 2023. Current advances in the diagnosis and treatment of sickle cell anaemia. Appl. Sci. (NIJBAS) 4.
Camerino, D.C., Tricarico, D., Desaphy, J.-F., 2007. Ion channel pharmacology. Neurotherapeutics. 4, 184–198.
Canver, M.C., Orkin, S.H., 2016. Customizing the genome as therapy for the β-hemoglobinopathies. Blood J. Am. Soc. Hematol. 127, 2536–2545.
Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., Julius, D., 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389, 816–824.
Cyril-Olutayo, M., Akinola, N., Temitope, A., Idris, A., Bejide, R., Agbedahunsi, J., 2020. In vitro antisickling and sub chronic toxicity studies of the ethanol extract of Cnidoscolus aconitifolius in Wistar Rats. Med. Aromat. Plants (Los Angeles) 9, 2167-0412.2120.
Dafaalla, E.A.A., Humeida, A.A.K., 2021. The effect of fixed oil extracts of Nigella sativa on sickle cells: an in-vitro study in Khartoum state-Sudan. World J. Adv. Res. Rev. 10, 317–321.
Danladi, S., Lawal, N.B., Alhassan, A.M., 2021. Review on the phytochemical and pharmcological activities of Hymenocardia acida tul (phyllantaceae). J. Current Biomed. Res. 1, 92–105.
Dellemijn, P.L., Fields, H.L., 1994. Do benzodiazepines have a role in chronic pain management? Pain 57, 137–152.
Diop, S., Pirenne, F., 2021. Transfusion and sickle cell anemia in Africa. Transfusion Clinique et Biologique 28, 143–145.
Djote, W., Kotue, T., Mafogang, B., Ngo, S., Pieme, A., 2020. Antisickling, antioxidant properties, fatty acids and vitamin E compositions of Azadirachta Indica J. seed oil used to manage sickle cell disease (SCD) in North Cameroon. J. Nutr. Food Lipid Sci. 1, 86–93.
Dormandy, E., James, J., Inusa, B., Rees, D., 2018. How many people have sickle cell disease in the UK? J. Public Health (Bangkok) 40, e291–e295.
Dufu, K., Alt, C., Strutt, S., Tang, T., Liao-Zou, H., Yuan, Y., Cathers, B.E., Oksenberg, D., 2020. GBT021601 inhibits HbS polymerization, prevents RBC sickling and improves the pathophysiology of sickle cell disease in a murine model. Blood 136, 7–8.
Eaton, W.A., Bunn, H.F., 2017. Treating sickle cell disease by targeting HbS polymerization. Blood J. Am. Soc. Hematol. 129, 2719–2726.
Eleonore, N.L.E., Cumber, S.N., Charlotte, E.E., Lucas, E.E., Edgar, M.M.L., Nkfusai, C.N., Geh, M.M., Ngenge, B.M., Bede, F., Fomukong, N.H., 2020. Malaria in patients with sickle cell anaemia: burden, risk factors and outcome at the Laquintinie hospital, Cameroon. BMC. Infect. Dis. 20, 1–8.
Eleutério, R., Nascimento, F.O., Araújo, T.G., Castro, M.F., Eleutério, J., Elias, D.B., Lemes, R.P., 2019. Double-blind clinical trial of arginine supplementation in the treatment of adult patients with sickle cell anaemia. Adv. Hematol. 2019.
Elufioye, T.O., Williams, B.M., Cyril-Olutayo, M.C., 2020. Identification of the anti-sickling activity of Anogeissus leiocarpus and in silico investigation of some of its phytochemicals. Avicenna J. Med. Biochem. 8, 1–14.
Elusiyan, C.A., Ayoade, O., Adeloye, A.O., Olorunmola, F.O., Agbedahunsi, J.M., Ogundaini, A.O., 2018. Antisickling and radical scavenging activities of selected medicinal plants and compounds from Mitracarpus villosus (Sw.) DC. Cham. Eur. J. Med. Plant 24, 1–10.
Esoh, K., Wonkam-Tingang, E., Wonkam, A., 2021. Sickle cell disease in sub-Saharan Africa: transferable strategies for prevention and care. Lancet Haematol. 8, e744–e755.
Fall, A.B., Vanhaelen-Fastré, R., Vanhaelen, M., Lo, I., Toppet, M., Ferster, A., Fondu, P., 1999. In vitro antisickling activity of a rearranged limonoid isolated from Khaya senegalensis. Planta Med. 65, 209–212.
Fathallah, H., Atweh, G.F., 2006. Induction of fetal hemoglobin in the treatment of sickle cell disease. In: ASH Education Program Book, 2006, pp. 58–62.
Ferrone, F.A., 2016. GBT440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. Br. J. Haematol. 174, 499–500.
Grosse, S.D., Odame, I., Atrash, H.K., Amendah, D.D., Piel, F.B., Williams, T.N., 2011. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am. J. Prev. Med. 41, S398–S405.
Han, J., Saraf, S.L., Gordeuk, V.R., 2020. Systematic review of voxelotor: a first-in-class sickle hemoglobin polymerization inhibitor for management of sickle cell disease. Pharmacotherapy 40, 525–534.
Hassell, K.L., 2010. Population estimates of sickle cell disease in the US. Am. J. Prev. Med. 38, S512–S521.
Hassell, K.L., 2016. Sickle cell disease: a continued call to action. Am. J. Prev. Med. 51, S1–S2.
Hazzazi, A.A., Ageeli, M.H., Alfaqih, A.M., Jaafari, A.A., Malhan, H.M., Bakkar, M.M., 2020. Epidemiology and characteristics of sickle cell patients admitted to hospitals in Jazan region, Saudi Arabia. J. Appl. Hematol. 11, 10–14.
Henneberg, R., Otuki, M.F., Furman, A.E.F., Hermann, P., Nascimento, A.J.d., Leonart, M.S.S., 2013. Protective effect of flavonoids against reactive oxygen species production in sickle cell anemia patients treated with hydroxyurea. Rev. Bras. Hematol. Hemoter. 35, 52–55.
Hernández-Salinas, G., Luna-Cavazos, M., Soto-Estrada, A., García-Pérez, E., Pérez-Vázquez, A., Córdova-Téllez, L., 2022. Distribution and eco-geographic characterization of Carica papaya L. native to Mexico. Genet. Resour. Crop. Evol. 69, 99–116.
Hockham, C., Bhatt, S., Colah, R., Mukherjee, M.B., Penman, B.S., Gupta, S., Piel, F.B., 2018. The spatial epidemiology of sickle-cell anaemia in India. Sci. Rep. 8, 17685.
Ibrahim, H., Sani, F., Danladi, B., Ahmadu, A., 2007. Phytochemical and antisickling studies of the leaves of Hymenocardia acida Tul (Euphorbiaceae). Pakistan J. Biol. Sci.: PJBS 10, 788–791.
Ikechukwu, E.L., Okafor, P.N., Egba, S.I., 2020. In vitro assessment of the anti-sickling properties of Buchholzia coriacea and Mucuna pruriens seed extracts. In Vitro Cellular Dev. Biol. Animal 56, 773–782.
Imaga, N., 2010. The use of phytomedicines as effective therapeutic agents in sickle cell anemia. Scientif. Res. Essays 5, 3803–3807.
Imaga, N., Gbenle, G., Okochi, V., Adenekan, S., Edeoghon, S., Kehinde, M., Bamiro, S., Ajiboye, A., Obinna, A., 2010. Antisickling and toxicological profiles of leaf and stem of Parquetina nigrescens L.
Imaga, N., Gbenle, G., Okochi, V., Akanbi, S., Edeoghon, S., Oigbochie, V., Kehinde, M., Bamiro, S., 2009. Antisickling property of Carica papaya leaf extract. Afr. J. Biochem. Res. 3, 102–106.
Imaga, N.A., Taiwo, O., 2017. Different therapeutic intervention and mechanisms of action of antisickling agents currently in use in sickle cell disease management.
Iyekowa, O., Okieimen, F., Ehisuoria, C.O., 2023. In-vitro antisickling activity of Pergularia daemia, Canna indica and Petiveria alliacea Plants used in the treatment of Sickle Cell Anaemia in Edo State. Nigeria. Tanzania J. Sci. 49, 433–445.
Jancso, G., Kiraly, E., JANCSÓ-GÁBOR, A., 1977. Pharmacologically induced selective degeneration of chemosensitive primary sensory neurones. Nature 270, 741–743.
Jastaniah, W., 2011. Epidemiology of sickle cell disease in Saudi Arabia. Ann. Saudi. Med. 31, 289–293.
Joel, A.-A., Mireille, K.K.T., Mattieu, K.A.K., Ange, K.G.K.N.D., Marcelin, K.K.A., Sitapha, O., Julien, G.K., Yvette, F., Ibrahime, S., Antoinette, Y.-C.C.C., 2023. Phytochemical investigation and antisickling properties of a Poly-herbal formula on the HBSS Red Blood Cells. J. Pharmacogn. Phytochem. 12, 260–265.
Kalish, B.T., Matte, A., Andolfo, I., Iolascon, A., Weinberg, O., Ghigo, A., Cimino, J., Siciliano, A., Hirsch, E., Federti, E., 2015. Dietary ω-3 fatty acids protect against vasculopathy in a transgenic mouse model of sickle cell disease. Haematologica 100, 870.
Kato, G.J., Piel, F.B., Reid, C.D., Gaston, M.H., Ohene-Frempong, K., Krishnamurti, L., Smith, W.R., Panepinto, J.A., Weatherall, D.J., Costa, F.F., 2018. Sickle cell disease. Nature Rev. Dis. Primers 4, 1–22.
Kavanagh, P.L., Fasipe, T.A., Wun, T., 2022. Sickle cell disease: a review. JAMa 328, 57–68.
Khamees, I., Ata, F., Choudry, H., Soliman, A.T., De Sanctis, V., Yassin, M.A., 2021. Manifestations of HbSE sickle cell disease: a systematic review. J. Transl. Med. 19, 262.
Kinney, T.R., Helms, R.W., O'Branski, E.E., Ohene-Frempong, K., Wang, W., Daeschner, C., Vichinsky, E., Redding-Lallinger, R., Gee, B., Platt, O.S., 1999. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Blood J. Am. Soc. Hematol. 94, 1550–1554.
Kirkham, F.J., Lagunju, I.A., 2021. Epidemiology of stroke in sickle cell disease. J. Clin. Med. 10, 4232.
Macharia, A.W., Mochamah, G., Uyoga, S., Ndila, C.M., Nyutu, G., Makale, J., Tendwa, M., Nyatichi, E., Ojal, J., Shebe, M., 2018. The clinical epidemiology of sickle cell anemia In Africa. Am. J. Hematol. 93, 363–370.
Mandal, A.K., Mitra, A., Das, R., 2020. Sickle cell hemoglobin. Vertebrate and invertebrate respiratory proteins. Lipoproteins Other Body Fluid Proteins 297–322.
Marwah, S., Wheelwright, D., Blann, A., Rea, C., Beresford, R., Phillips, J.D., Wright, J., Bareford, D., 2001. Vitamin E correlates inversely with non-transferrin-bound iron in sickle cell disease. Br. J. Haematol. 114, 917–919.
McGann, P.T., 2014. Sickle cell anemia: an underappreciated and unaddressed contributor to global childhood mortality. J. Pediatr. 165, 18–22.
Mehanna, A., 2001. Sickle cell anemia and antisickling agents then and now. Curr. Med. Chem. 8, 79–88.
Melamed, D., Nov, Y., Malik, A., Yakass, M.B., Bolotin, E., Shemer, R., Hiadzi, E.K., Skorecki, K.L., Livnat, A., 2022. De novo mutation rates at the single-mutation resolution in a human HBB gene region associated with adaptation and genetic disease. Genome Res. 32, 488–498.
Metcalf, B., Chuang, C., Dufu, K., Patel, M.P., Silva-Garcia, A., Johnson, C., Lu, Q., Partridge, J.R., Patskovska, L., Patskovsky, Y., 2017. Discovery of GBT440, an orally bioavailable R-state stabilizer of sickle cell hemoglobin. ACS. Med. Chem. Lett. 8, 321–326.
Mishra, S., Sonter, S., Dwivedi, M.K., Singh, P.K., 2021. Anti-sickling, anti-inflammatory and anti-oxidant potential of Rubia cordifolia L.: A traditionally used medicinal plant of Amarkantak, Madhya Pradesh (India). Medicinal Plants-Int. J. Phytomed. Rel. Ind. 13, 499–514.
Misra, H., Bainbridge, J., Berryman, J., Abuchowski, A., Galvez, K.M., Uribe, L.F., Hernandez, A.L., Sosa, N.R., 2017. A Phase Ib open label, randomized, safety study of SANGUINATE™ in patients with sickle cell anemia. Rev. Bras. Hematol. Hemoter. 39, 20–27.

Mojisola, C.-O.C., Anthony, E.A., Alani, D.M., 2009. Antisickling properties of the fermented mixture of Carica papaya Linn and Sorghum bicolor (L.) Moench. Afr. J. Pharm. Pharmacol. 3, 140–143.
Mojisola, O.C., Adebolu, E.A., Alani, D.M., 2008. Antisickling properties of Carica papaya Linn. J. Nat. Prod. 1, 56–58.
Mota, F.M., Ferreira Júnior, M.A., Cardoso, A.I.d.Q., Pompeo, C.M., Frota, O.P., Tsuha, D. H., Souza, A.S.d., 2022. Analysis of the temporal trend of mortality from sickle cell anemia in Brazil. Rev. Bras. Enferm. 75, e20210640.
Mpiana, P., Mudogo, V., Tshibangu, D., Ngbolua, K., Shetonde, O., Mangwala, P., Mavakala, B., 2007. In vitro antisickling activity of anthocyanins extracts of a Congolese plant: Alchornea cordifolia M. Arg. J. Med. Sci. 7, 1182–1186.
Ngbolua, K., Mpiana, P., Tshibangu, D., Mazasa, P., Gbolo, B., Atibu, E., Kadima, J., Kasali, F., 2014. In vitro antisickling and radical scavenging activities of a poly-herbal formula (Drepanoalpha®) in sickle cell erythrocyteand acute toxicity study in wistar albino rats. European. J. Med. Plants. 4, 1251.
Nilius, B., Vennekens, R., Owsianik, G., 2008. Vanilloid transient receptor potential cation channels: an overview. Curr. Pharm. Des. 14, 18–31.
Nurain, I.O., Bewaji, C.O., 2017. Interaction of some antisickling agents with human erythrocytes calcium pump. J. BioSci. Biotechnol. 6, 111–117.
Nurain, I.O., Bewaji, C.O., Johnson, J.S., Davenport, R.D., Zhang, Y., 2017. Potential of three ethnomedicinal plants as antisickling agents. Mol. Pharm. 14, 172–182.
Nwaoguikpe, R.N., 2010. The phytochemical, proximate and amino acid compositions of the extracts of two varieties of tiger nut (Cyperus esculentus) and their effects on sickle cell hemoglobin polymerization. J. Med. Med. Sci. 1, 543–549.
Oder, E., Safo, M.K., Abdulmalik, O., Kato, G.J., 2016. New developments in anti-sickling agents: can drugs directly prevent the polymerization of sickle haemoglobin in vivo? Br. J. Haematol. 175, 24–30.
Oduola, T., Adeniyi, F., Ogunyemi, E., Bello, I., Idowu, T., 2006. Antisickling agent in an extract of unripe pawpaw (Carica papaya): is it real? Afr. J. Biotechnol. 5.
Oduola, T., Adeniyi, F., Ogunyemi, E., Bello, I., Idowu, T., Subair, H., 2007a. Toxicity studies on an unripe Carica papaya aqueous extract: biochemical and haematological effects in wistar albino rats. J. Med. Plants Res. 1, 001–004.
Oduola, T., Adeniyi, F., Ogunyemi, E., Idowu, T., Bello, I., 2007b. Evaluation of the effects of intake of extract of unripe pawpaw (Carica papaya) on liver function in sickle cell patients. World J. Med. Sci. 2, 28–32.
Ogoda Onah, J., Akubue, P.I., Okide, G.B., 2002. The kinetics of reversal of pre-sickled erythrocytes by the aqueous extract of Cajanus cajan seeds. Phytother. Res. 16, 748–750.
Ohnishi, S.T., Ohnishi, T., Ogunmola, G.B., 2001. Green tea extract and aged garlic extract inhibit anion transport and sickle cell dehydration in vitro. Blood Cells Molecules Dis. 27, 148–157.
Okpuzor, J., Adebesin, O., Ogbunugafor, H., Amadi, I., 2021. The potential of medicinal plants in sickle cell disease control: a review. Int. J. Biomed. Health Sci. 4.
Olushola-Siedoks, A.A.-M., Igbo, U.E., Asieba, G., Damola, I.A., Igwe, C.C., 2020. GC-MS aided In silico molecular docking studies on the anti-sickling properties of Zanthoxylum zanthoxyloides (Lam.) Zepern. & Timler stem bark. J. Pharmacogn. Phytochem. 9, 08–18.
Ouattara, B., Angenot, L., Guissou, P., Fondu, P., Dubois, J., Frédérich, M., Jansen, O., Van Heugen, J.-C., Wauters, J.-N., Tits, M., 2004. LC/MS/NMR analysis of isomeric divanilloylquinic acids from the root bark of Fagara zanthoxyloides Lam. Phytochemistry 65, 1145–1151.
Pal, D., Mishra, P., Sachan, N., Ghosh, A.K., 2011. Biological activities and medicinal properties of Cajanus cajan (L) Millsp. J. Adv. Pharm. Technol. Res. 2, 207.
Payne, A.B., Mehal, J.M., Chapman, C., Haberling, D.L., Richardson, L.C., Bean, C.J., Hooper, W.C., 2020. Trends in sickle cell disease–related mortality in the United States, 1979 to 2017. Ann. Emerg. Med. 76, S28–S36.
Pecker, L.H., Schaefer, B.A., Luchtman-Jones, L., 2017. Knowledge insufficient: the management of haemoglobin SC disease. Br. J. Haematol. 176, 515–526.
Piel, F.B., Rees, D.C., DeBaun, M.R., Nnodu, O., Ranque, B., Thompson, A.A., Ware, R.E., Abboud, M.R., Abraham, A., Ambrose, E.E., 2023. Defining global strategies to improve outcomes in sickle cell disease: a. Lancet Haematol. Commission 10, e633–e686.
Pierre, L., Moses, N., Peter, C., 2015. Structure activity relationship (SAR) of some benzoic acid derivatives from plant origin that exhibit anti-sickling properties in vitro. Nat. Prod. Chem. Res. 3, 2.
Pompeo, C.M., Ferreira Junior, M.A., Cardoso, A.I.d.Q., Souza, M.d.C., Frota, O.P., Mota, F.M., Ivo, M.L., 2022. Clinical-epidemiological characteristics and mortality in patients with sickle cell anemia: a retrospective cohort study of 1980 at 2018. Int. J. Gen. Med. 1057–1074.
Quinn, C.T., Rogers, Z.R., McCavit, T.L., Buchanan, G.R., 2010. Improved survival of children and adolescents with sickle cell disease. Blood J. Am. Soc. Hematol. 115, 3447–3452.
Rathore, S., Prashant, V., Prashant, D., Nath, A., Shivram, A., 2023. Screening of phytochemicals for antisickling effects. Res. J. Pharmacy Technol. 16, 5790–5795.
Rees, D.C., Williams, T.N., Gladwin, M.T., 2010. Sickle-cell disease. The Lancet 376, 2018-2031.
Safo, M.K., Abdulmalik, O., Danso-Danquah, R., Burnett, J.C., Nokuri, S., Joshi, G.S., Musayev, F.N., Asakura, T., Abraham, D.J., 2004. Structural basis for the potent antisickling effect of a novel class of five-membered heterocyclic aldehydic compounds. J. Med. Chem. 47, 4665–4676.
Safo, M.K., Ahmed, M.H., Ghatge, M.S., Boyiri, T., 2011. Hemoglobin–ligand binding: Understanding Hb function and allostery on atomic level. Biochimica et Biophysica Acta (BBA)-Proteins Proteomics 1814, 797–809.
Safo, M.K., Bruno, S., 2011. Allosteric effectors of hemoglobin: past, present and future. Chem. Biochem. Oxygen Therapeutics 285–300.
Safo, M.K., Kato, G.J., 2014. Therapeutic strategies to alter the oxygen affinity of sickle hemoglobin. Hematol./Oncol. Clinics 28, 217–231.
Salih, K.M., 2019. The impact of sickle cell anemia on the quality of life of sicklers at school age. J. Family. Med. Prim. Care 8, 468–471.
Sani, I., Ukwuani, K., Haruna, M., 2021. Ethnobotanical survey and in vitro antisickling effect of some selected medicinal plants. Asian J. Res. Biochem. 9, 1–14.
Santo, A.H., 2022. Sickle cell disease related mortality in Brazil, 2000-2018. Hematol. Transfus. Cell Ther. 44, 177–185.
Santos, F.M., Terra, G., Monte, M.A., Chaer, G.M., 2022. Growth, yield and stem form of young African mahoganies (Khaya spp.) in mixed-species plantations and successional agroforestry systems. New. For. (Dordr) 53, 181–202.
Saraf, S.L., Abdullahi, S.U., Akinsete, A.M., Fasola, F.A., Idowu, M., Pennington, S., Ershler, W.B., Stagg, M.P., Chin, W., Zimmerman, E., 2023. Preliminary results from a multicenter phase 2/3 study of next-generation HbS polymerization inhibitor GBT021601 for the treatment of patients with sickle cell disease. Blood 142, 274.
Smith, W.R., Bauserman, R.L., Ballas, S.K., McCarthy, W.F., Steinberg, M.H., Swerdlow, P.S., Waclawiw, M.A., Barton, B.A., Anemia, I.o.t.M.S.o.H.i.S.C., 2009. Climatic and geographic temporal patterns of pain in the Multicenter Study of Hydroxyurea. Pain. 146, 91–98.
Snyder, A.B., 2022. Surveillance for sickle cell disease—sickle cell data collection program, two states, 2004–2018. MMWR. Surveillance Summaries 71.
Steinberg, M.H., 2008. Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. Scientific World Journal. 8, 1295–1324.
Steinberg, M.H., Barton, F., Castro, O., Pegelow, C.H., Ballas, S.K., Kutlar, A., Orringer, E., Bellevue, R., Olivieri, N., Eckman, J., 2003. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMa 289, 1645–1651.
Stuart, M.J., Nagel, R.L., 2004. Sickle-cell disease. The Lancet 364, 1343–1360.
Szallasi, A., Cortright, D.N., Blum, C.A., Eid, S.R., 2007. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nature Rev. Drug Discov. 6, 357–372.
Szolcsányi, J., 1993. Capsaicin in the Study of Pain. Academic, London, pp. 1–26.
Teguem Tchoulegheu, A., Nya Nkwikeu, P.J., Lena Yembeau, N., Choupo, A.C., Nkenmeni Djamnou, C., Feudjio, A.F., Chetcha Chemegni, B., Biapa Nya, P.C., Pieme, C.A., 2023. Antisickling and antihemolytic mechanism of Spirulina platensis (Oscillatoriaceae): a nutraceutical commonly used in Cameroon. Evid.-Based Compl. Altern. Med. 2023.
Teixeira, S., Cortellazzi, L., Grotto, H., 2003. Effect of hydroxyurea on G gamma chain fetal hemoglobin synthesis by sickle-cell disease patients. Brazilian J. Med. Biol. Res. 36, 1289–1292.
Telfer, P., Coen, P., Chakravorty, S., Wilkey, O., Evans, J., Newell, H., Smalling, B., Amos, R., Stephens, A., Rogers, D., 2007. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica 92, 905–912.
Thangaswamy, S., Branch, C.A., Ambadipudi, K., Acharya, S.A., 2021. Quercetin completely ameliorates hypoxia–reoxygenation-induced pathophysiology severity in NY1DD transgenic sickle mice: intrinsic mild steady state pathophysiology of the disease in NY1DD is also reversed. Biomolecules 11, 1473.
Tshilanda, D.D., Onyamboko, D.N., Babady-Bila, P., Ngbolua, K.-t.-N., Tshibangu, D.S., dia Fita Dibwe, E., Mpiana, P.T., 2015. Anti-sickling activity of ursolic acid isolated from the leaves of Ocimum gratissimum L.(Lamiaceae). Nat. Prod. Bioprospect. 5, 215–221.
Uyoga, S., Macharia, A.W., Mochamah, G., Ndila, C.M., Nyutu, G., Makale, J., Tendwa, M., Nyatichi, E., Ojal, J., Otiende, M., 2019. The epidemiology of sickle cell disease in children recruited in infancy in Kilifi, Kenya: a prospective cohort study. Lancet Glob. Health 7, e1458–e1466.
Valverde, Y., Benson, B., Gupta, M., Gupta, K., 2016. Spinal glial activation and oxidative stress are alleviated by treatment with curcumin or coenzyme Q in sickle mice. Haematologica 101, e44.
Venkatachalam, K., Montell, C., 2007. TRP channels. Annu. Rev. Biochem. 76, 387–417.
Vierstra, J., Reik, A., Chang, K.-H., Stehling-Sun, S., Zhou, Y., Hinkley, S.J., Paschon, D. E., Zhang, L., Psatha, N., Bendana, Y.R., 2015. Functional footprinting of regulatory DNA. Nat. Methods 12, 927–930.
Yawn, B.P., Buchanan, G.R., Afenyi-Annan, A.N., Ballas, S.K., Hassell, K.L., James, A.H., Jordan, L., Lanzkron, S.M., Lottenberg, R., Savage, W.J., 2014. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMa 312, 1033–1048.
Zhang, S., Li, P., Wei, Z., Cheng, Y., Liu, J., Yang, Y., Wang, Y., Mu, Z., 2022. Cyperus (Cyperus esculentus L.): a review of its compositions, medical efficacy, antibacterial activity and allelopathic potentials. Plants 11, 1127.
Zu, Y.-g., Liu, X.-l., Fu, Y.-j., Wu, N., Kong, Y., Wink, M., 2010. Chemical composition of the SFE-CO2 extracts from Cajanus cajan (L.) Huth and their antimicrobial activity in vitro and in vivo. Phytomedicine 17, 1095–1101.