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Sickle hemoglobin polymerization inhibition and antisickling medicinal plants

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ABSTRACT

Sickle cell disease (SCD) is a dilapidating disorder that is associated with organ destruction and decreased life expectancy. Therapeutic remedies that lead to fundamental cure of SCD such as, bone marrow and stem cell transplantations, as well as gene replacement therapy, are very costly and unaffordable to the disease sufferers in developing countries. In regions where these therapeutic approaches are possible, there are also limitations such as immunologic transplant rejection, difficulty in prognosis, difficulty in obtaining a suitable donor, end-organ dysfunction, and adverse health effects, especially among the older sufferers of this disease. The eagerness of researchers to develop new drugs for the amelioration of the crisis associated with SCD and a possible cure of the disease has led to the discovery of biomolecular agents that inhibit the mechanisms of HbS polymerization as well as medicinal plants with antisickling potentials. The antisickling potency of medicinal plants should be harnessed through research funding and efforts geared towards the discovery of molecules in such plants with HbS polymerization inhibitory effects.

Keywords: Antisickling, erythrocyte, HbS polymerization, Medicinal plants, Membrane stability.

INTRODUCTION

Sickle cell disease (SCD) is an inherited chronic disorder that is characterized by a crescent-shaped erythrocyte in place of the disc-shaped type[1]. SCD is a reoccurring disorder in various regions of the world and has been a disease of great concern to the public health sector [2, 3]. Regions reported with high incidence include Africa, the Arabian Peninsula, some parts of Southern Europe and Asia, while low occurrence level has been recorded in Greece, Italy, India and the Middle East [4]. SCD is a dilapidating disorder that is associated with organ destruction and decreased life expectancy [5, 6].

The sickle hemoglobin (HbS) variant arises as a result of a point mutation that disrupts the sequence of coding of the β-globin gene, in which adenine replaces thymine followed by the displacement of adenine by uracil in the triplet code through a partially acceptable missense mutation [7, 8]. Hydrophobic valine replaces the hydrophilic glutamic acid in the mutant gene; this substitution takes place exactly at the β_6 globin position. The R group of the hydrophobic β_6 valine of a deoxygenated sickle hemoglobin (deoxy-HbS) binds to the hydrophobic pocket formed by leucine (β_{88}), phenylalanine (β_{85}) and aspartic acid (β_{73}) on the neighboring deoxy-HbS [9-11]. This inter-hydrophobic interaction induces the nucleation of deoxy-HbS and assemblage into low soluble microfibril polymers which stresses the interior erythrocyte membrane, causing erythrocyte destabilization and deformation to a sickle shape [7,12].

Approximately 20–25 million people suffer from SCD globally, and about 300,000 children are given birth yearly with SCD [13-15]. The management of SCD is usually channeled towards the use of prophylaxis in conjunction with drugs that mitigate the symptoms, without any fundamental cure [12]. Therapeutic remedies that lead to fundamental cure of SCD such as, bone marrow and stem cell transplantations, as well as gene replacement therapy, are very costly and unaffordable to the disease sufferers in developing countries [15]. In regions where these therapeutic approaches are possible, there are also limitations such as immunologic transplant rejection, difficulty in prognosis, difficulty in obtaining a suitable donor, end-organ dysfunction, and adverse health effects, especially among the older sufferers of this disease [6, 15, 16].

This present review was channeled towards the description of the biochemical basis of 4 mechanisms associated with the inhibition of HbS polymerization as well as medicinal plants that have been investigated to possess antisickling effects in conjunction with bioactive compounds that have been investigated to elicit this effect.

Sickle hemoglobin polymerization inhibition mechanisms

The polymerization of deoxy-HbS in SCD results to the generation of insoluble fibers that lead to

erythrocyte sickling. As discussed earlier, HbS polymerization occurs following the stereo-specific binding of the β_6 valine isopropyl group with the hydrophobic pocket of another HbS tetramer. Thus, the inhibition of HbS polymerization is possible through 4 major mechanisms as discussed below.

Increasing oxygen affinity

The 2- state allosteric Monod-Wyman-Changeux (MWC) model can be used to describe the influence of oxygen on HbS polymerization [17, 18]. This model tries to illustrate an equilibrium that exists between the T quaternary structure (a low oxygen affinity arrangement of the 4 subunits of fully deoxygenated hemoglobin) and the R quaternary structure (a high affinity arrangement of fully oxygenated hemoglobin) [19, 20]. The MWC model strongly suggests that HbS polymerization can be hindered *in vivo* by adjusting the T-R equilibrium in the direction of R [21].

The mechanisms involved are presented in Figures 1, 2 and 3. There is a shift in the T-R equilibrium along the direction of R following the preferential binding of a small molecule, such as a drug (indicated in red colour in figure 1). The change from the T to R –states takes place through ~15° relative rotation of αβ dimmers (Figure 1). Only HbS in the T quaternary structure (empty circles) can enter the sickle fiber and thus undergo polymerization, while HbS in the R quaternary conformation (filled circles) does not enter the sickle fiber and thus does not undergo polymerization (Figure 2). The sickle fibers is characterized by a diameter of 21 nm, and consist of 14 strands that are made up of 7 helically twisted strand pairs, as seen in deoxy-HbS X-ray structure [22]. In the oxygen binding curves illustrated in Figure 3, there is a left shift, an indication of an increase in oxygen affinity, after the drug preferential binding to the R quaternary structure [17, 18, 23].

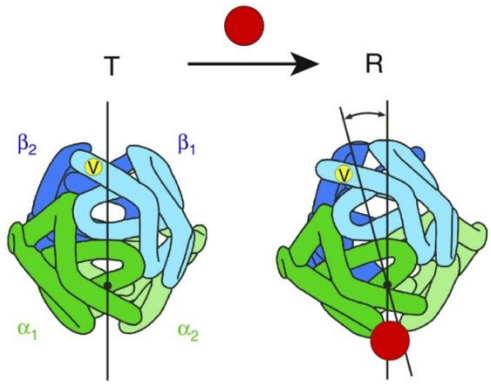

Figure 1: Hemoglobin existing in a rapidly reversible equilibrium between the T and R quaternary conformations [17, 18]

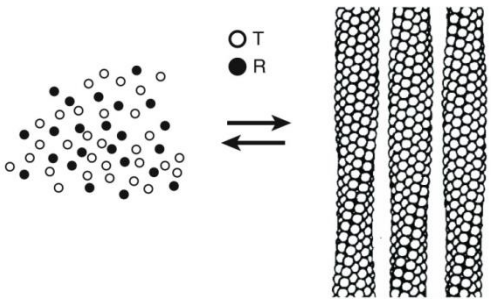

Figure 2: Cartoon of polymerization equilibrium [23]

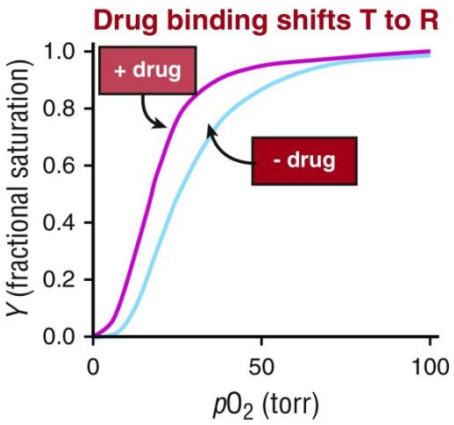

Figure 3: Oxygen binding curves [22]

Reduction in the concentration of 2,3-diphosphoglycerate (2,3-DPG)

2,3-DPG exerts three major effects on the polymerization of HbS and is regarded as the main allosteric effector for hemoglobin [24-26]. 2,3-DPG reduces the affinity for oxygen through adjusting the T-R quaternary equilibrium in the direction of T by binding in the cleft separating the β subunits of HbS (Figure 4). Therefore, decreasing the concentration of 2,3-DPG will elevate HbS fraction in the R quaternary conformation, leading to inhibition in HbS polymerization [27] (Figure 5). 2,3-DPG has been reported to induce the stabilization of the sickle fiber, and thus ameliorates the level of the dissolution of HbS [28]. Reduction in the concentration of 2,3-DPG is associated with an elevation in intracellular pH through the Gibbs-Donnan equilibrium [29]. An increase in pH is accompanied by an increase in the solubility of deoxy-HbS and therefore reduces the rate of polymerization [30].

2,3-DPG levels in red blood cell (RBC) can be reduced through the use of drugs or compounds that inhibit enzymatic pathways that lead to an increase in the synthesis of 2,3-DPG. Certain anions, phosphoglycerate, etc. elicit such action [31].

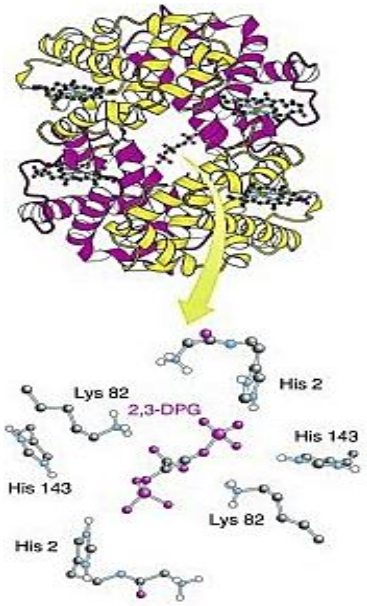

Figure 4: 2,3-DPG binding in the cleft between the β (yellow) subunits of the T quaternary structure [22]

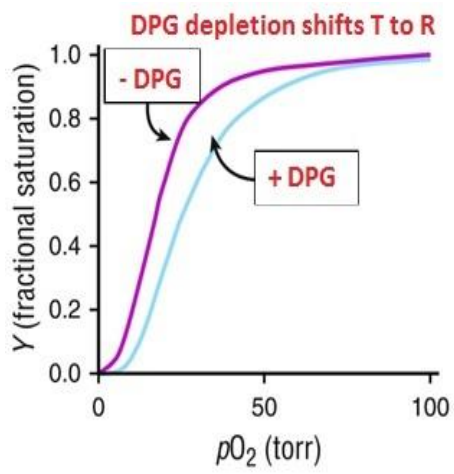

Figure 5: Shifting of the T-R quaternary equilibrium in the direction of R due to a decrease in the concentration of 2,3-DPG [22].

Blocking intermolecular contacts in the sickle fiber

The formation of fiber in HbS takes place following the binding together of hemoglobin molecules. One of the major approaches towards the treatment of sickle cell disease is to identify a small molecule with high binding affinity for the HbS site that is involved in intermolecular contact in the sickle fiber. There are three major problems associated with the use of this approach, these include:

i. The molecule or drug must possess high binding specificity for the HbS (Figure 6); a covalent bonding is required in order to reduce the amount of the molecule or drug needed for bonding.
ii. However, the hemoglobin molecule is made up of smooth surfaces with no high depth clefts or crevices that can give room for any strong non-covalent bonding [22, 32].
iii. Taking into consideration the average intra-erythrocytic quantity of HbS molecule, a very large quantity of the molecule or drug would be required for effective and efficient binding to the receptor sites of the HbS molecules [22].

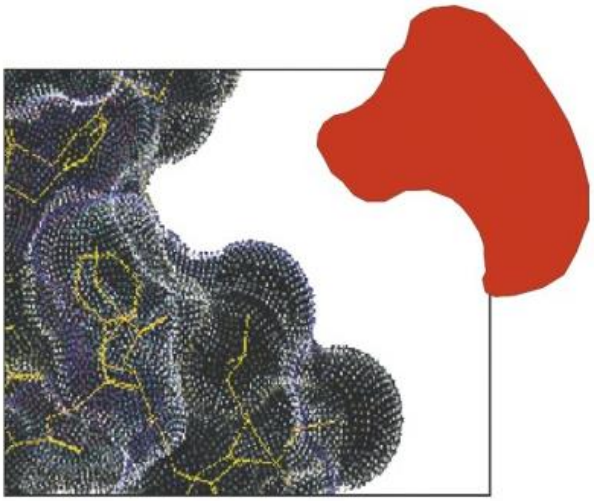

Figure 6: Small molecule inhibitor or drug (in red colour) that could fit and bind covalently into the shallow acceptor site of the hemoglobin molecule [22]

Inducing the synthesis of fetal Hemoglobin (HbF)

HbF ($\alpha_2\gamma_2$) is the major protein responsible for the distribution of oxygen in the fetus within the last months of development of the embryo as well as few months after birth. HbF disrupts the polymerization of HbS ($\alpha_2\beta^S{}_2$) by reducing the intracellular concentration of HbS and thus plays a beneficial role in the amelioration of the vaso-occlusive crisis associated with SCD. Hydroxyurea and 5-azacytidine are the major pharmacological agents known to induce the synthesis of HbF and thus increases HbF per F cell [33], although the toxic effects imposed by these drugs have been reported [12].

The mechanism for the reduction of intracellular HbS concentration by HbF takes place as follows: the HbS homo-tetramer $\alpha_2\beta^S{}_2$ dissociates into dimers αβ, followed by HbS and HbF random re-association in 3 tetramers in a binomial distribution to yield the sickle-fetal hybrid $\alpha_2\gamma\beta^S$, thereby reducing HbS $\alpha_2\beta^S{}_2$ homo-tetramer fraction (Figure 7), although this process is quite more complex than described above [34, 35].

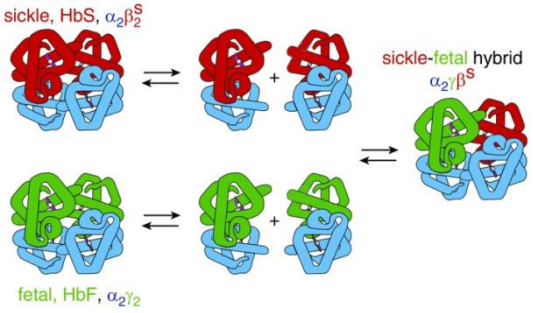

Figure 7: Reduction of intracellular HbS ($\alpha_2\beta^S{}_2$) concentration by HbF ($\alpha_2\gamma_2$) [22]

Antisickling effects of medicinal plants

The use of medicinal plants or herbs is preferred by many for the treatment of diseases due to the lesser toxic side effects associated with its use. Antisickling medicinal plants found in different regions of the world were reported in this study (Table 1), with major concern on the plant part, extract/fraction and compounds responsible for the antisickling effect, as well as their mechanisms of action. Sodium metabisulfite ($Na_2S_2O_5$), a reducing agent that induces low oxygen levels, is usually used by researchers to initiate the polymerization of deoxy-HbS *in vitro* inorder to carry out studies on the effect of medicinal plants on HbS polymerization [36-38].

***Adansonia digitata* (Malvaceae) [39]**

The anthocyanins extract of *A. digitata* bark was able to stabilize the membrane of sickle erythrocytes, and induced the reduction of methemoglobin to hemoglobin, thus an indication of the antisickling activity of this plant extract. This plant extract elicited an antisickling effect with a maximal sickle cell normalization rate of 65.7%, and a minimum normalization concentration of 5.0 mg/mL.

***Anacardium occidentale* (Anacardiaceae), *Psidium guajava* (Myrtaceae) *and Terminalia catappa* (Combretaceae) [12, 40-42]**

Petroleum ether and ethylacetate leaf extracts of both *A. occidentale* and *T. catappa*, as well as the *n*-hexane extract of *P. guajava* leaf exhibited membrane stabilization effects. The phytocomponents, namely trans-13-octadecenoic acid, pentacosane, 3-pentadecyl ester, hexadecanoic acid, 11-octadecenoic acid, dibutyl phthalate, and methyl ester were the major bioactive compounds responsible for this effect. The aqueous leaf extracts of these plants also possessed

erythrocyte membrane stabilizing potency, although 800 mg/dL of *A. occidentale* initiated destabilization of the sickled erythrocyte membranes. The bioactive compounds phthalates, methylated esters, aliphatic alcohols, cycloalkanes, cyclo-alcohols, aminated sugars, methylated fatty acids, aliphatic hydrocarbons, nitro-compounds, D-erythro-sphinganine, isothiocyanates, aromatic derivatives in the ethylacetate, chloroform, n-hexane and petroleum ether leaf extracts of these plants inhibited the polymerization of HbS. The aqueous extracts of these plants also exhibited polymerization inhibitory effect in a dose and time dependent manner.

***Cajanus cajan* (Fabaceae) and *Zanthoxylum zanthoxyloides* (Rutaceae) [43]**

The potency of the aqueous extracts of *Z. zanthoxyloides* leaf and *C. cajan* seed and leaf to induce resistance of sickled erythrocytes hemolysis as well as inhibit the polymerization of HbS was studied. *Z. zanthoxyloides* leaf, *C. cajan* seed and *C. cajan* leaf extracts decreased the percentage of sickle cells from an initial control level of 91.6% to 38.2%, 41.7% and 32.8% respectively, and their rate of inhibition of sickle erythrocyte polymerization were 6.6×10^{-2}, 5.9×10^{-2} and 8.0×10^{-2} respectively. These plant extracts also hindered the hemolysis of erythrocytes by decreasing the number of hemolyzed cells from 100% to 0%. Bioactive compounds, including alkaloids, tannins, glycosides, saponins and flavonoids were observed to be present in all the plant extracts.

***Calliandra portoricensis* (Fabaceae) [44]**

The ethanolic and aqueous extracts of *C. portorincensis* roots and leaves produced sickled erythrocyte membrane stabilizing effect in a concentration dependent manner as these plant extracts were able to elicit almost the same effect with the standard drug, ibuprofen. The ethanolic root extract of this plant produced the highest effect.

***Carica papaya* (Caricaceae) [43, 45, 46]**

The aqueous extract of *C. papaya* leaf exerted membrane stabilizing effect on sickled RBC, as this plant extract was able to reverse sickled erythrocytes. This effect was attributed to the presence of the bioactive compounds, namely: saponins, alkaloids, tannins, glycosides and flavonoids identified in the leaf extract of this plant. The aqueous extract of *C. papaya* leaf possessed a polymerization inhibition rate of 6.0×10^{-2}, as well as decreased the percentage of sickled cells from the control percentage of 91.6% to 47.6%, and increased the resistance of erythrocytes to hemolysis by decreasing the level of hemolyzed cells from 100% to 0%. The chloroform, ethyl acetate and aqueous extracts of the green and brown leaves of this plant also inhibited the polymerization of HbS. The chloroform extract gave the highest effect while the aqueous extract gave the lowest effect.

***Elaesis guineensis* (Arecaceae) [47]**

The aqueous extract of *E. guineensis* flower has shown great efficacy in the maintenance of the integrity of the RBC membrane and also mitigated its hemolysis. 80 mg/mL, 100 mg/mL and 120 mg/mL concentrations of the aqueous flower extract of this plant inhibited erythrocyte sickling processes through the obstruction of HbSS gelation, although 20 mg/mL, 40 mg/mL and 60 mg/mL concentration of this plant extract supported the polymerization of sickled erythrocytes. All the concentrations decreased the mean corpuscular fragility levels of the sickled erythrocytes when compared with the control.

***Ganoderma lucidum* (Ganodermataceae) [48]**

The aqueous extract of *G. lucidum* reversed and stabilized the integrity and morphology of sickled erythrocyte membrane and prevented hemolysis. Erythrocyte that were administered 5 mg/mL of extract at 9.0 g/L and 7.0 g/L saline concentrations produced the lowest percentage lysis of 6.15 ± 1.96% and 6.76 ± 1.63% respectively. There was a dose dependent increase in the stabilization of the erythrocyte membrane as the erythrocyte percentage stabilities of 5 mg/mL, 10 mg/mL and 15 mg/mL of extracts were 12.92 ± 0.86%, 26.91 ± 1.05% and 28.81 ± 0.94% respectively. The 15 mg/mL extract had the highest reduction rate of hemoglobin polymerization as well as the least red blood cell deformity score.

Mishenland polyherbal extract [49]

The Mishenland polyherbal extract (a combination *S. bicolor* leaves, *U. afzelii* roots, *M. charantia* leaves and seeds, *S. longepedunculat* root barks, *D. guineense* leaves and barks, and *P. amarus* leaves) was reported to have intensified sickled erythrocyte membrane stabilization, inhibited hemolysis as well as prevented the polymerization of HbS in a dose dependent manner, these are indications of the antisickling effect of this polyherbal formula. The compounds, namely: glycosides, saponins, terpenoids, alkaloids, phenols and tannin were identified in this herbal formulation and are thus responsible for its antisickling effect.

***Monodora myristica* (Annonaceae) and *Helianthus annuus* (Asteraceae) [50]**

The antisickling effects of the benzene soluble, crude aqueous, water soluble, and alcohol extract fractions of these plants has been confirmed. *H. annuus* benzene soluble extract fraction gave the highest polymerization inhibition rate of HbSS (89.15%). The water soluble extract fraction of *H. annuus* had the highest sickling reversal effect among the plant extracts. The antisickling efficacy of the alcoholic extract of these plants was attributed to the presence of certain lipophillic amino acids.

***Moringa oleifera* (Moringaceae) [51]**

The water soluble fraction, fat soluble fraction and butanol-soluble fraction of *M. oleifera* leaf have been reported to hinder the polymerization of sickle cell hemoglobin, elevate the Fe^{2+}/Fe^{3+} ratio thereby promoting the erythrocyte oxidant status. The rate of inhibition of HbS polymerization by the water-soluble leaf fraction was 88.80%, while 98.35% was recorded for both the fat-soluble and butanol-soluble leaf fractions. Various antisickling amino acids (arginine, histidine, lysine, tryptophan, and phenylalanine) as well as ascorbic acid were identified to be present in the leaf extract of this plant.

***Mucuna pruriens* (Fabaceae) [52]**

The methanol extract of *M. pruriens* leaf elicited membrane stabilizing effect on sickle erythrocytes as well as exhibited antioxidant effects. The percentage (%) inhibition of sickle erythrocyte hemolysis by this plant extract at 100, 200, 400, 600 and 800 mg/mL concentrations was observed to be dose dependent, and the phytochemical screening result reported the presence of flavonoids, terpenoids, anthraquinones, alkaloids, saponins, tannins and cardiac glycosides.

***Newbouldia laevis* (Bignoniaceae) [53]**

The hydro-ethanolic extracts of the roots and stem barks of this plant deter the hemolysis of sickled erythrocytes, thereby maintaining membrane stability. These plant extracts were reported to mitigate the rate of sickling at 17% and 16% by the roots and stem barks extracts respectively against 78% for the control. Polyphenols from hydro-ethanolic extracts of *N. laevis* were identified to be responsible for the sustenance of sickle erythrocytes membrane integrity and stability.

***Phaseolus vulgaris* (Fabaceae) [54]**

The amino acids extract of *P. vulgaris* seed at a concentration of 12 mg/mL inhibited HbS gelation, increased oxyhemoglobin levels as well as regulated the action of three membrane-bound ATPases (increased Na^+/K^+ and Ca^{2+}-ATPases and reduced Mg^{2+}-ATPase), indicating that this plant possesses antisickling potentials. The least inhibition effect offered by the amino acid extracts was 39.98 ± 2% while the highest inhibition effect was 71.16 ± 2%.

***Trema orientalis* (Cannabaceae) [55]**

Anthocyanins leaf extracts of *T. orientalis* hindered the hypoxic induced hemolysis of sickled erythrocytes, increased the solubility of deoxy-HbS, as well as inhibited the intracellular polymerization of sickle hemoglobin. This plant extract restored the normal biconcave shape of sickled erythrocytes with a radius value of 3.5 ± 0.2 µm. There was an increase in the solubility of deoxy-HbS following the administration of this plant extract.

***Zanthoxyllum heitzii* (Rutaceae) [56]**

The aqueous fruit extract of *Z. heitzii* supported the stabilization of sickled erythrocyte membranes at 250 µg/mL induced by 2% sodium metabisulfite. $Na_2S_2O_5$ was used to raise the erythrocyte sickling level from 29.62 to 55.46% in 2 hours. Administration of the aqueous extract mitigated the percentage of sickling cells. The antioxidant and anti-radical efficacies of the extract was also ascertained. Phytocomponent groups identified to be responsible for the membrane stabilization of *Z. heitzii* were the phenolics and alkaloids.

***Zanthoxylum macrophylla* (Rutaceae) [57]**

The aqueous extract of the roots of *Z. macrophylla* has shown erythrocyte membrane stabilization effect, and also reversed sickling induced by 2% $Na_2S_2O_5$. The percentage stabilization of the sickle erythrocyte membrane by this plant extract, calculated from the mean corpuscular fragility values, was 14.39%; while its sickling reversing effect was equivalent to that observed with another known antisickling compound, phenylalanine, at a concentration of 400 µM.

Table 1: Antisickling effects of medicinal plants

Plant (family)	Plant Part used for study	Extract/fraction	Potent compounds	Mechanism of action	References
Adansonia digitata (Malvaceae)	Bark	Anthocyanin	Not reported	Stabilization of sickled erythrocyte membrane, inducing the reduction of methemoglobin to hemoglobin	[39]
Anacardium occidentale (Anacardiaceae), *Psidium guajava* (Myrtaceae) and *Terminalia catappa* (Combretaceae)	Leaf	Petroleum ether, ethylacetate, n-hexane, chloroform, aqueous	Phthalates, methylated esters, aliphatic alcohols, cycloalkanes, cyclo-alcohols, aminated sugars, methylated fattyacids, aliphatic hydrocarbons, nitro-compounds, D-erythro-sphinganine, isothiocyanates, aromatic derivatives, trans-13-octadecenoic acid, pentacosane, 3-pentadecyl ester, hexadecanoic acid and 11-octadecenoic acid	Membrane stabilization of sickled erythrocyte, inhibition of HbS polymerization	[12, 40-42]
Cajanus cajan (Fabaceae) and *Zanthoxylum zanthoxyloides* (Rutaceae)	Seed and leaf	Aqueous	Alkaloids, tannins, glycosides, saponins and flavonoids	Inhibition of both sickled erythrocyte hemolysis and HbS polymerization	[43]
Calliandra portoricensis (Fabaceae)	Roots and leaves	Ethanol and aqueous	Not reported	Sickled erythrocyte membrane stabilization	[44]
Carica papaya (Caricaceae)	Leaf	Chloroform, ethylacetate and aqueous	Saponins, alkaloids, tannins, glycosides and flavonoids	Reversal of sickled erythrocytes, HbS polymerization inhibition and induction of erythrocyte resistance to hemolysis	[43, 45, 46]
Elaesis guineensis (Arecaceae)	Flower	Aqueous	Not reported	Maintenance of erythrocyte membrane integrity and obstruction of hemolysis, inhibition of HbSS gelation.	[47]
Ganoderma lucidum (Ganodermataceae)	Whole plant	Aqueous	Not reported	Inhibition of both erythrocyte hemolysis and HbS polymerization, sickled erythrocyte	[48]

				membrane stabilization	
Mishenland polyherbal extract (combination of *Sorghum bicolor* leaves, *Uvaria afzelii* roots, *Momordica charantia* leaves and seeds, *Securidaca longipedunculata* root barks, *Dialium guineense* leaves and barks, and *Phyllanthus amarus* leaves)	Leaf, seed, bark and root	Not reported	Glycosides, saponins, terpenoids, alkaloids, phenols and tannin	Sickled erythrocyte membrane stabilization, hemolysis inhibition and disruption of HbS polymerization	[49]
Monodora myristica (Annonaceae) and *Helianthus annuus* (Asteraceae)	Whole plant	Benzene soluble, crude aqueous, water soluble and alcohol	Lipophillic amino acids	HbS polymerization inhibition, and sickling reversal effect	[50]
Moringa oleifera (Moringaceae)	Leaf	Water soluble, fat soluble and butanol-soluble	Arginine, histidine, lysine, tryptophan, phenylalanine and ascorbic acid	Inhibition of the polymerization of HbS, elevation of Fe^{2+}/Fe^{3+} ratio to promote the erythrocyte oxidant status	[51]
Mucuna pruriens (Fabaceae)	Leaf	Methanol	Flavonoids, terpenoids, anthraquinones, alkaloids, saponins, tannins and cardiac glycosides	Membrane stabilizing effect on sickle erythrocytes, antioxidant effects and inhibition of sickled erythrocyte hemolysis	[52]
Newbouldia laevis (Bignoniaceae)	Root and stem bark	Hydro-ethanol	Polyphenols	Maintenance of sickled erythrocyte membrane stability and inhibition of hemolysis	[53]
Phaseolus vulgaris (Fabaceae)	Seed	Amino acids	Not reported	Inhibition of HbS gelation, increased oxyhemoglobin levels and regulation of the action of three membrane-bound ATPases	[54]
Trema orientalis (Cannabaceae)	Leaf	Anthocyanins	Not reported	Inhibition of the hypoxic induced hemolysis of sickle erythrocytes, increasing the solubility of deoxy-HbS, inhibition of the intracellular polymerization of HbS and the restoration of the normal biconcave shape of sickled erythrocytes	[55]
Zanthoxyllum heitzii (Rutaceae)	Fruit	Aqueous	Phenolics and alkaloids	Antioxidant effects, HbS polymerization inhibition and Sickle erythrocyte membrane stabilization	[56]
Zanthoxylum macrophylla (Rutaceae)	Root	Aqueous	Phenylalanine	Erythrocyte membrane stabilization and sickling reversal effects	[57]

CONCLUSION AND RECOMMENDATIONS

The eagerness of researchers to develop new drugs for the amelioration of the crisis associated with SCD and a possible cure of the disease has led to the discovery of biomolecular agents that inhibit the mechanisms of HbS polymerization as well as medicinal plants with antisickling potentials. Thus, 4 major HbS polymerization inhibition mechanisms and 25 medicinal plants with antisickling potentials have been reported in this work. The antisickling potency of medicinal plants should be harnessed through research funding and efforts geared towards the discovery of molecules in such plants with HbS polymerization inhibitory effects.

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