Chapter from the book *Sickle Cell Disease - Pain and Common Chronic Complications*

Chapter 13

Phytotherapy and the Relevance of Some Endogenous Antioxidant Enzymes in Management of Sickle Cell Diseases

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Abstract

Introduction: Sickle cell disease (SCD) is one of the most devastating diseases ravaging most populations.

Methodology, results, and discussion: The numerous plants earlier reported to be used for treating SCD were compiled along with their geographical locations (using relevant online databases when not provided in cited articles for each plant) and relative antisickling strength. The process of hemolysis in sickle cell diseases, a brief overview of the current treatments, and management of sickle cell diseases is considered in the chapter. The activities of endogenous antioxidants and some biochemical enzyme markers coupled to these plants' ability to maintain the integrity of red blood cell membrane are discussed in line with their antisickling health benefits and are also used to proffer more reliable molecular therapeutic strategies for managing sickle cell diseases. Furthermore, the operational principles of some enzymes, as well as their contributions to advancement of knowledge for management of the disease, were examined.

Conclusion: Geographical spread of these identified antisickling plants contributes to low levels of sickle cell patients where the potentials are known. More efforts should therefore be channeled toward increasing awareness about the plants, as well as harnessing their active principles to obtain a more lasting solution to sickle cell disease at the molecular level.

Keywords: plants, sickle cell diseases, enzymes, antisickling, antioxidants

1. Introduction

Sickle cell disease (SCD) is an autosomal recessive genetic disorder that is caused by a mutation in the β-globin gene on chromosome 11q [1]. This mutation involves glutamic acid being substituted with valine at the 6th position along the β-globin chain. $\alpha_2\beta_2$ is expressed as normal hemoglobin, $\alpha_2\beta^S$ (heterozygote) is expressed as sickle trait, while α_2S_2 (homozygote recessive) is expressed as sickle cell anemia. Most of the time as a result of repeated series of sickling and unsickling, the erythrocytes become permanently damaged and consequently lyse. Some acute and chronic tissue injuries result when these abnormally shaped red cells impede blood flow through the vessels [2].

Sickle cell disease is one of the most devastating diseases ravaging most populations. It is a disease that affects numerous nations and ethnic groups. It is associated with painful symptoms and is a genetic disease in which an individual inherits the allele for sickle cell hemoglobin from both parents. Patients with this disease possess lower level of erythrocytes than the normal healthy human. In addition to an unusually large number of immature cells such as transferrin receptor-positive, reticulocytes, erythroblasts that sometimes manifest in the form of granular bodies in the cytoplasm of red blood cells, the blood contains many long, thin, crescent-shaped erythrocytes that look like the blade of a sickle [3]. The hemoglobin (hemoglobin S) in blood of patients with sickle cell disease becomes insoluble and forms polymers that aggregate into tubular fibers when deoxygenated. The altered properties of hemoglobin S result from a single amino acid substitution, which leads to the presence of a valine (Val) with no electric charge instead of a glutamate (Glu) residue with a negative charge when pH is 7.4 at position 6 in the two chains, resulting in two fewer negative charges than normal hemoglobin A [3]. Glutamine residue replaces the valine residue at position 6 of β-chain of hemoglobin in the normal blood to form a "sticky" hydrophobic interaction outside the surface of the sickle cell blood. It is the resultant sticky points on the surface of sickle cell blood that makes deoxyhemoglobin S molecules to interact abnormally with each other to form the long, fibrous aggregates peculiar to this disorder that eventually cause the deformation of the normal disc biconcave red blood cell 'RBC' [4].

Polymerization of the sickled cells thereby alters the integrity of the red cell membrane, leading to loss of K^+, water, and a corresponding gain of Na^+. Increased intracellular free Ca^{2+} occurs during sickling, resulting in a loss of K^+ with accompanying movements of Cl^- and water [5]. The clumping of sickled RBCs leads to blockage of small blood vessels, preventing blood supply to various organs. The deoxygenation process in tissue capillaries causes damage to its endothelium, leading to exudation of plasma into the surrounding soft tissue [6]. The integrity of the red blood cell membrane is maintained by hydration and sickling is generated when there is dehydration of the membrane. It is also believed that increase in synthesis of endogenous nitric oxide may be beneficial to SCD patients by preventing the mopping up of the nitric oxide by the hemoglobin released during hemolysis, which may trigger a cascade of events that ultimately inhibit blood flow [7].

There is high incidence of the sickle cell disease in different parts of the world, especially in Africa and Asia. The traditional people in these regions have learnt to manage the problem using plants which are God's gift of nature, especially among the lower socio-economic class who cannot afford the high cost of western medicine, as well as traditionalists who simply believe in their efficacy [6]. There has been increasing insight into gaining understanding about the management approaches of sickle cell disease in several African countries on the efficacy of conventional and traditional medicines. However, no substantial evidence exists to support the efficacy of herbal medications in actually curing the disease. Research into phytotherapy of diseases is a current trend in the management of sickle cell disease, with the hope of finding inexpensive and less toxic alternative medicines that people can easily access [8].

Nutritional evaluation of *S. monostachyus* leaves revealed the presence of carbohydrate, protein, ash, fiber, and fat as well as potassium and vitamin C in higher concentrations; calcium, magnesium, vitamin A, vitamin B_6, vitamin E in lower concentrations; and others in trace quantities. Phytochemical screening revealed the presence of tannins, saponins, alkaloids, flavonoids, cyanogenic glycosides, and phytate [9]. Caffeic acid is one of the bioactive phenolic components of *Solenostemon monostachyus* leaves (unpublished report). It is a potent antioxidant. The study of antioxidants especially in various antisickling agents is of great significance because antisickling agents vary in their degree of efficacy. Antioxidants constitute a major component of these antisickling agents; thus, it is believed that the higher the antioxidant property of an antisickling agent, the higher its possible antisickling and therapeutic effect. Thus, reducing oxidative stress may ameliorate sickle cell crisis [8].

As a reference point, African/Nigerian medicinal plants are applied in the treatment of diseases, such as HIV/AIDS, malaria, tuberculosis, sickle cell diseases, diabetes, mental disorders, and so on. Research on these medicinal plants has shown various results such as antimicrobial (16%), molluscicidal (11%), antimalarial (7%), plant toxicology (7%), antitumor (4%), and many others. The major challenge with these medicinal plants is the lack of scientifically based evidence, quality standards, and regulations [6]. The antisickling activity of *S. monostachyus* on human sickle blood cells resulting in the alleviation of SCD symptoms has been reported [10]. Sickle cell disease and thalassemia are hemoglobinopathies characterized by chronic hemolysis [11].

2. Contribution of phytomedicine in the management of sickle cell diseases

The use of medicinal plants in the control of many diseases such as sickle cell diseases may be useful, especially in developing countries. The cost of treatment provided by orthodox medical practitioners largely contributes to the dependence on the use of traditional medicine in low-income settings. Much of the medicinal use of plants seems to have been developed through observations of wild animals, and by trial and error. It has been estimated by the World Health Organization that 80% of the world's population relies on traditional medicine to meet their daily health needs. Thiocyanate-rich foods, erythropoietin, nutritional supplements, food extracts, phytochemicals, and synthetic compounds have been tested in vitro and in vivo on their possible roles in the management of sickle cell disease [12]. Many medicinal plants with antisickling properties are indicated in **Table 1**. The leaves from most of the above-identified plants have been successfully proven to play a role in the management of sickle cell diseases possibly by antioxidant phytochemicals, proximate nutrients, amino acids, and minerals. Phytochemical testing revealed the presence of folic acid, vitamin B12, alkaloids, spooning, glycosides, tannins, and anthraquinones. Studies also indicated the plant extracts contained flavonoids and the antioxidants vitamins A and C [13, 14].

S.n	Natural antisickling resources	Name of country where identified	Natural habitat and geographical locations	References
1	*Zanthoxylum zanthoxyloides* (Fagara) root	Nigeria	Senegal and other west African countries	[23]
2	*Cajanus cajan* seeds	Nigeria	West/South Africa, southern India, and northern Australia	[24, 25]
3	*Solenostemon monostachyus* (P. Beauv.) Briq.	Nigeria	Anthrogenic habitat and rocky savanna in Cameroon, Gabon, Equatorial Guinea, Ivory Coast, Benin, Nigeria, Liberia, Guinea, Ghana, Togo, Burkina Faso, Republic of the Congo, Sao Tome and Principe, Central African Republic, Mali, and Brazil	[10]
4	*Ipomea involucrata*	Nigeria	Tropical Asia (possibly India); South and South-East Asia, tropical Africa, South and Central America; and Oceania	[10]
5	*Carica papaya* seed oil	Nigeria	Originated in Central America and is now grown in tropical areas worldwide	[10]
6	*Carica papaya* unripe fruit	Nigeria	Originated in Central America and is now grown in tropical areas worldwide	[13, 26]
7	*Parquetina nigrescens* (whole plant extracts) with ability to boost blood volume	Nigeria	A large part of Africa, from Senegal east to Sudan and south through Central and East Africa to Zambia, Angola and eastern Zimbabwe	[27]
8	Nicosan (drug)	Nigeria	Commercially distributed by National Institute for Pharmaceutical Research and Development (NIPRD), Nigeria	[8, 15, 19, 28]
9	Ciklavit (drug)	Nigeria	Commercially distributed by Neimeth International Pharmaceuticals Plc, Lagos, Nigeria	[8, 24, 29, 30]
10	*Walthera indica* (Malvaceae)	Nigeria	Widely distributed across tropical part of the world.	
11	Dried fish (Tilapia) and dried prawn (*Astacus red*)	Nigeria	Globally	[31–33]
12	Fermented *Sorghum bicolor* leaves	Nigeria	Widely cultivated in tropical part of Africa and Asia	[12]
13	*Terminalia catappa* (Tropica Almond)	Nigeria	Well-distributed globally but has abundant presence in regions between Seychelles and India; Southeast Asia; Papua New Guinea and Northern Australia; South Pacific Region; China, Taiwan, Cambodia, and New Caledonia	[12]
14	*Scoparia dulcis* Linnaeus	Nigeria	Tropical America and South-East Asia	[34]

S.n	Natural antisickling resources	Name of country where identified	Natural habitat and geographical locations	References
15	*Zanthoxylum macrophylla* (aqueous extract of roots)	Nigeria	Savannah and dry forest vegetation of Southwestern Nigeria	[35, 36]
16	*Garcinia kola* (aqueous extracts)	Nigeria	Tropical rain forests with moist lowland especially in part of west Africa	[37, 38]
17	*Adansonia digitata* (bark)	Nigeria	Africa, Madagascar, and Australia	[37, 39]
18	*Fagara zanthoxyloides* (root extracts)	Nigeria	West Africa and Cameroon	[40, 41]
19	*Vernonia amygdalina* (extracts)	Nigeria	Tropical Africa and Asia	[42]
20	*Parquetina nigrescens*	Nigeria	Most part of Africa	
21	Grape (*Citrus paradise*)	Nigeria	Tropical and subtropical part of the world	[10]
22	Lemon grass (*Citrus lemon*)	Nigeria	Widely distributed globally particularly in Mediterranean region	
23	Pumpkin, *Telfeira occidentalis* (fresh leaves)	Nigeria	Forest zone of West and Central Africa, particularly in Benin (Nigeria) and Cameroon	[8]
24	*Pterocarpus santolinoides* DC	Nigeria	Africa and South America	[43]
25	*Aloe vera*	Nigeria	Indigenous to most parts of Africa, widely distributed in the tropical and subtropical regions of the world	[43]
26	*Alchornea cordifolia*	Democratic Republic of Congo	West and Central Africa	[44–47]
27	*Afromomum albo violaceum*	Democratic Republic of Congo	West and Central Africa	[48]
28	*Annona senegalensis*	Democratic Republic of Congo	West and Central Africa.	[49]
29	*Cymbopogon densiflorus*	Democratic Republic of Congo	Widely distributed across the globe	[50]
30	*Bridelia ferruginea*	Democratic Republic of Congo	West Africa	[50]
31	*Ceiba pentandra*	Democratic Republic of Congo	Tropical regions of America and Africa	[50]
32	*Morinda lucida*	Democratic Republic of Congo	West and Central Africa	[50]
33	*Hymenocardia acida*	Democratic Republic of Congo	Tropical region of Africa	[50]

S.n	Natural antisickling resources	Name of country where identified	Natural habitat and geographical locations	References
34	*Coleus kilimandcharis*	Democratic Republic of Congo	Subtropical and warm temperate region of India, Nepal, Myanmar, Sri Lanka, Thailand, and Africa	[50–52]
35	*Dacryodes edulis*	Democratic Republic of Congo	Rainforests of Central and West Africa, particularly Angola, Benin, Cameroon, Central African Republic, Congo, Cote d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Gabon, Ghana, Liberia, Nigeria, Sierra Leone, Togo, and Uganda	[50]
36	*Caloncoba welwithsii*	Democratic Republic of Congo	Tropical forest of Africa, particularly in West Africa	[50]
37	*Vigna unguiculata*	Democratic Republic of Congo	Originated in Africa. Present across the globe particularly in savanna regions of West and Central Africa	[50]

Table 1. Geographical locations of some identified antisickling plants.

The use of phytomaterials such as *Piper guineense, Pterocarpus osun*, *Eugenia caryophyllata*, and *Sorghum bicolor* extracts in the drug Nicosan, previously NIPRISAN (Nix-0699), for the treatment of sickle cell disease was reported to possess antisickling properties. Nicosan was developed by a research team led by Prof. Charles O. Wambebe at the National Institute for Pharmaceutical Research and Development, Abuja, Nigeria. The efficacy of the drug had been reported with minor fear of toxicity since the constituents are largely from commonly consumed food items such as *Piper guineense, Eugenia caryophyllata*, and *Pterocarpus osun* [15–19]. A major constituent of a herbal formula (Ajawaron HF) consists of the extracts of the roots of *Cssus populnea* L. CPK had also been effectively used to reverse sickling in the management of sickle cell disease in south west of Nigeria. The most prominent and widely used of them all is Ciklavit developed by Prof G. Ekeke after 18 years of intensive research in collaboration with Neimeth Pharmaceuticals, Lagos, Nigeria. These efforts led to the development of WHO-approved drugs such as Niprisan and Ciklavit from some of these plants traditionally identified for treating sickle cell diseases [8, 20, 21].

The role of other components in Ciklavit (apart from *Cajanus cajan*) is essentially nutritional. A study on children with sickle cell disease suggests that nutritional supplements can help improve growth and weight gain. It can also boost the immune system and thus help in protecting against bacterial infections. Zinc deficiency is a major nutritional problem seen in sickle cell disease [8, 22]. Also reported are amino acids, glycine, phenylalanine, and tyrosine, which have been reported to possess antisickling properties. Particularly, extracts from underutilized plants such as *S. monostachyus*, *Carica papaya* seed oil, and *Ipomoea involucrata* were proven to reverse human sickle cell blood almost completely coupled with the ability to also reduce stress in sickle cell disease patients. Hence, each plant individually or in combination can be used in the management of sickle cell disease [10].

Local mixtures of herbivores, pollinators, and micro-organisms generated from the application of plants usually upregulate or downregulate certain biochemical pathways. These actions are often a result of their secondary metabolites as well as pigments, which can be refined to produce drugs [53]. Many drugs originally derived from plants, such as salicylic acid (a precursor of aspirin) originally derived from white willow bark and the meadowsweet plant, have been developed using this approach. Quinine—antimalarial drug, Vincristine—an anticancer drug, and drugs (morphine, codine, and paregoric) for treating diarrhea were developed from Cinchona bark, periwinkle, and the opium poppy, respectively [54].

3. Plants as sources of antioxidants in the management of sickle cell diseases

In addition to depletion in iron level, the generation of reactive oxygen species (ROS) in the erythrocytes is a major factor contributing to the occurrence of anemia in sickle cell diseases. ROS are defined as substances generated by one electron reduction of molecular oxygen, including oxygen radicals and reactive nitrogen species (RNS) [55]. Common radical species include peroxide, superoxide, and the hydroxyl radical that contain an unpaired electron and as such are extremely reactive, allowing them to react immediately with any biological molecule to produce cellular damage. ROS contributes to the pathogenesis of several hereditary disorders of erythrocytes, including sickle cell disease, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Oxidative stress is defined as the imbalance between pro-oxidants and antioxidants, which is a result of the formation of reactive oxygen species (ROS) in excess of the capacity of antioxidants to remove them [56].

3.1. Antioxidants

Antioxidants are the first line of defense against free radical damage and are critically needed for the maintenance and optimization of human health and well-being. Defence mechanisms against free radical-induced oxidative stress involve: (i) preventative mechanisms, (ii) repair mechanisms, (iii) physical defenses, and (iv) antioxidant defences. The body is also equipped with natural enzymatic antioxidant defences that include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Antioxidants terminate these chain reactions by removing free radical intermediates and inhibit other oxidation reactions (**Figure 1**). They do this by being oxidized themselves, so antioxidants are often reducing agents such as thiols, ascorbic acid, or polyphenols [57].

In order to protect the cells and organ systems of the body against reactive oxygen species, a highly sophisticated and complex antioxidant protection system has been evolved by humans. This involves a variety of components such as nutrient-derived antioxidants, antioxidant enzymes, metal-binding proteins, and numerous other antioxidant phytonutrients, which are both endogenous and exogenous in origin, that function interactively and synergistically to neutralize free radicals [59]. The natural antioxidants are naturally occurring antioxidants having high or low molecular weights and can differ in their physical and chemical properties.

The mechanisms by which these antioxidants act at molecular and cellular levels include role in gene expression and regulation, apoptosis, and signal transduction. Thus, antioxidants are involved in fundamental metabolic and homeostatic processes [58]. General patterns of behavior of some endogenous antioxidant enzymes and other relevant enzymes associated with sickle cell disease patients are subsequently described to provide more insight into how to solve the numerous challenges of the disease. Furthermore, introduction to a few selected enzymes that uniquely interact with constituents in these medicinal plants and are more relevant to the advancement of sickle cell diseases are provided subsequently.

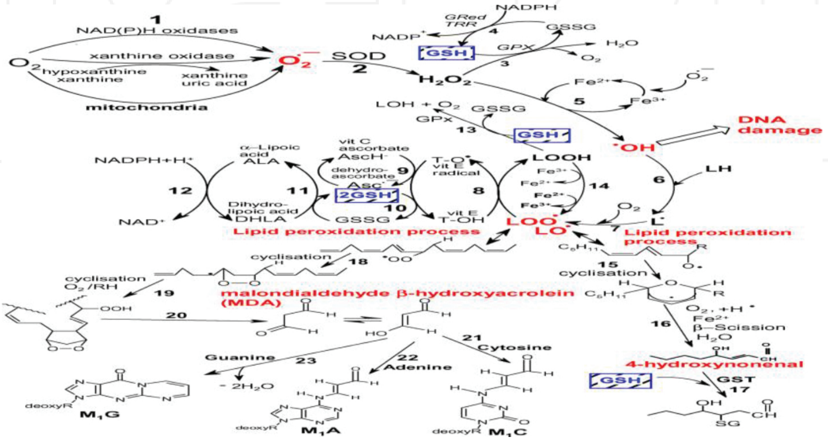

Figure 1. Pathways of ROS formation, the lipid peroxidation process, and the role of glutathione (GSH) and other antioxidants (vitamin E, vitamin C, lipoic acid) in the management of oxidative stress (equations are not balanced) [58].

3.2. Glucose-6-Phosphate Dehydrogenase (G6PD)

Glucose-6-phosphate dehydrogenase (G6PD) is the limiting enzyme that catalyzes the first reaction in the pentose phosphate pathway (**Figure 2**) in which glucose is converted into the pentose sugars required for glycolysis and various biosynthetic reactions. The pentose phosphate pathway (also known as the HMP shunt pathway) has a major biochemical role of providing reducing power to all cells in the form of NADPH (reduced form of nicotinamide adenine dinucleotide phosphate). This is possible in the presence of enzyme G6PD and 6-phosphogluconate dehydrogenase. NADPH enables cells to neutralize oxidative stress often induced by several oxidant agents and to preserve the reduced form of glutathione [57]. The hemoglobin in the blood, enzymes, and other proteins are damaged by the oxidants after all the leftover reduced glutathione is consumed. This leads to the generation of cross-bonding, protein deposition, and electrolyte imbalance in the red cell membranes. The hemoglobin from damaged red blood cells is metabolized to bilirubin that causes jaundice after attaining high concentrations [60]. High incidence of G6PD has been associated with areas of high prevalence of sickle cell disease. G6PD deficiency screening among SCD patients has provided the opportunity to administer appropriate preventive and therapeutic measures. The enzyme is becoming an increasingly strong confirmatory indicator of blood associated with sickle cell diseases and other closely associated ailments like malaria [10, 61]. The enzyme provides information on the link between malaria and sickle cell diseases so as to understand strategies for the adoption of resistance of SCD patients to malaria to improve human health.

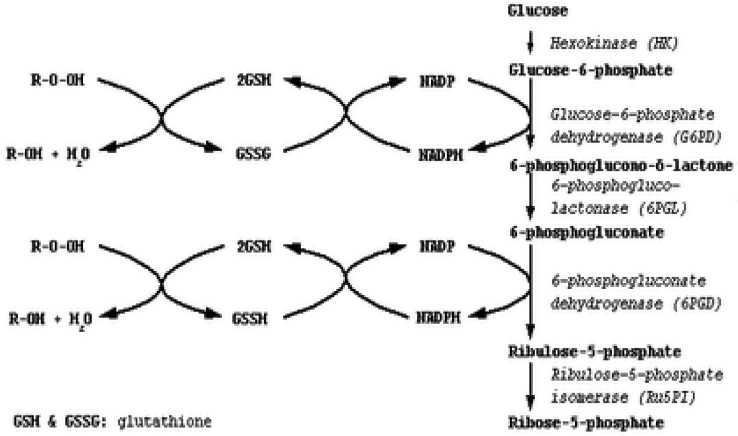

Figure 2. The pentose phosphate pathway. Source: [60].

3.3. Heme oxygenase

Heme oxygenases (HO) consists of a family of evolutionarily conserved endoplasmic reticulum (ER) enzymes [62]. Heme oxygenase (HO) plays a central role in regulating the levels of intracellular heme by catalyzing the oxidative degradation of heme into equimolar amounts of biliverdin, carbon monoxide, and iron as shown in **Figure 3a** and **b** [63]. They are central in determining what happens with regard to the central components of mammalian stress response and defense against oxidative stress [64]. Heme oxygenase activity is a key determinant of the health status of sickle cell anemia patients. Human sickle blood enhances endothelial heme oxygenase (HO) activity and the positive effects of HO-1 induction, biliverdin, and CO in reducing sickle blood adherence and in promoting vasodilation, indicating the need to further explore the therapeutic potentials of the HO pathway in the treatment of SCD [64]. The human HO-1 is comprised of a protein fold that primarily contains α-helices. The heme is held between two of these helices (**Figure 3b**). HO-1 acts as a cytoprotective stress protein and provides defense against oxidative stress associated with sickle cell disease by accelerating the degradation of pro-oxidant heme and hemo proteins to the radical scavenging bile pigments, biliverdin, and bilirubin [65]. HO-1 helps the body's defense in response to physical stress. The levels of heme are strictly controlled by the balance between heme biosynthesis and catabolism as indicated in **Figure 4** [65]. The key factor in the transcriptional activation of HO-1 is transcription factor Nrf2 (**Figure 4**). It interacts with many other genes that encode phase II drug-metabolizing enzymes so as to respond to oxidative stress [68].

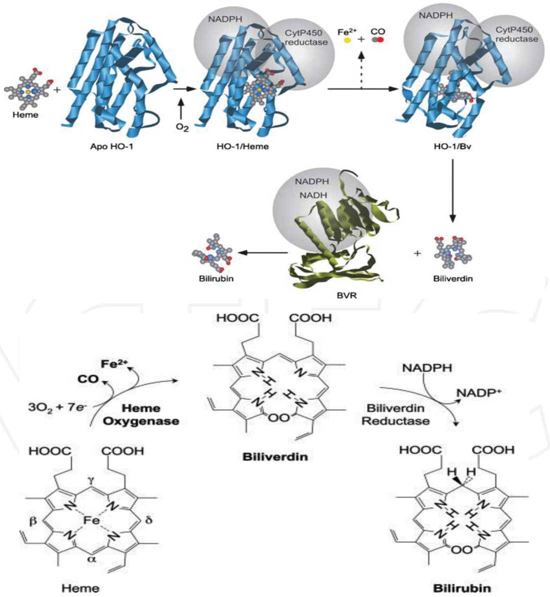

Figure 3. (a) The Heme oxygenase system. Source: [66]. (b) The Heme oxygenase system. Source: [67].

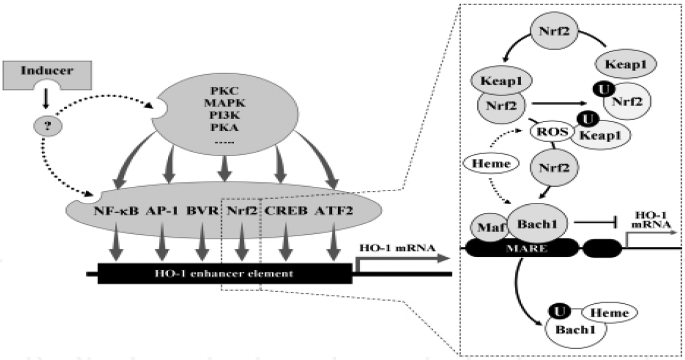

Figure 4. Regulation of HO-1 induction by transcription factors and kinases. Source: [69].

Sickle hemoglobin induces the expression of heme oxygenase-1 (HO-1) in hematopoietic cells through a mechanism that involves the ubiquitination-degradation of Kelch-like ECH-associated protein 1 (Keap1), a cytoplasmic repressor of the transcription factor NF-E2-related factor-2 (Nrf2). Upon nuclear translocation, Nrf2 binds to the stress-responsive elements in the Hmox1 promoter, a regulatory mechanism that plays a central role in the control of Hmox1 expression in response to heme [70]. Moreover, the higher rate of free heme released from sickle versus normal human subjects, in the absence of inflammation, induces HO-1 expression without causing cytotoxicity and this explains how sickle human Hb may also cause the expression of HO-1 in human and mouse peripheral blood mononuclear cells and in human endothelial cells as well [54]. Although a link between sickle cell disease and resistance to severe malaria is well established, the biochemical relationship between the two is unknown.

3.4. Inducible nitric oxide synthase

Nitric oxide (NO) also influences the outcome of sickle cell disease. This outcome may sometimes be beneficial to SCD patients, provided there is increase in the production of endogenous NO so as to prevent the release of hemoglobin during hemolysis [7]. Inducible nitric oxide synthase (iNOS) is not normally expressed in the cells, but can be induced by the action of bacterial endotoxins (lipopolysaccharide), cytokines, and other agents. Though it is mainly identified in macrophages, iNOS expression may be stimulated in virtually any cell or tissue type, provided the appropriate inducing agents have been identified [71]. Upon its expression, iNOS remains constantly active and independent of intracellular Ca^{2+} concentrations. Cell and tissue damage can be linked to the NO radical itself or NO interaction with $O_2^{-}\bullet$ resulting in the formation of peroxynitrite ($ONOO^-$). Most of the inflammatory and autoimmune lesions are characterized by large amounts of activated macrophages and neutrophils. NO can be secreted in large quantities by the cells, causing damage to the surrounding tissues [72].

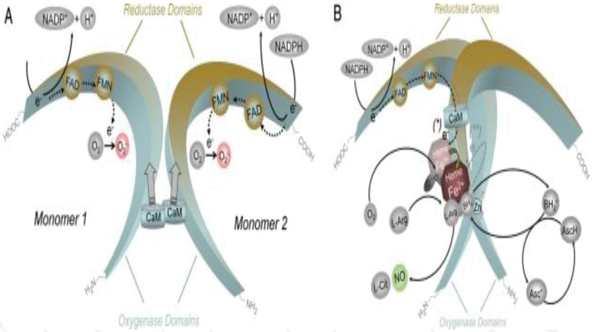

Figure 5. Structure of NOS monomers (A) and the functional dimer (B) Source: [71].

Finally, the excessive production of NO by iNOS plays a critical role in septic shock. This condition is characterized by massive microvascular lesions, arteriolar vasodilatation, and hypotension. Symptoms are usually initiated by bacterial endotoxins. Nonetheless, decrease in blood pressure can occur as a result of excessive production of NO by iNOS induced in the vascular wall [73]. In mammals, nitrous oxide (NO) is produced by the calcium-calmodulin-regulated constitutive isoenzymes eNOS (endothelial NOS) and nNOS (neuronal NOS), while the inducible isoform, iNOS, binds to calmodulin at physiologically significant concentrations producing NO free radicals as an immune defense mechanism (this is the direct cause of septic shock), and it may also play a role in autoimmune diseases. NOS-derived NO represents most of the NO produced in the vasculature and is associated with plasma membranes around cells including the membranes of red blood cells [71]. The structure and catalytic mechanisms of functional NOS are shown in **Figure 5**.

4. Conclusion

In conclusion, it is worthwhile to increase the search for potential plants that could supply bioactive compounds useful for the treatment of sickle cell disease. More so, concerted efforts are needed to further generate drugs to complement the already few drugs in existence, while taking into account the synergistic effect on these bioactives. This will help to standardize the administration of the bioactives to avoid any impediment to health due to overdose. Furthermore, it is necessary to exploit understanding of the interaction of these bioactives with the genes of sickle cell disease patient to increase our chances of getting a permanent solution to the disease. Geographical spread of these identified antisickling plants contributes to low levels of sickle cell patients where the potentials are known. More efforts should therefore be channeled toward increasing awareness about the plants.

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