International Blood Research & Reviews

Volume 15, Issue 1, Page 26-37, 2024; Article no.IBRR.112448
ISSN: 2321–7219

Afro Medicinal Plants a Promising Remedy for Sickle Cell Anemia

N E. Ahajumobi [a*] and J C. Asika [b]

[a] Department of Public Health, College of Health Science, Walden University, Minneapolis, USA.
[b] College of Nursing, Walden University, Minneapolis, USA.

Authors' contributions

This work was carried out in collaboration between both authors. Author NEA designed the study, performed the analysis, wrote the protocol, and wrote the first draft of the manuscript. Author NEA managed the analyses of the study and managed the literature searches. Author JCA participated in managing the analyses of the study and literature searches. Author JCA read and approved the final manuscript.

Article Information

DOI: 10.9734/IBRR/2024/v15i1332

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/112448

Systematic Review Article

Received: 24/11/2023
Accepted: 30/01/2024
Published: 23/02/2024

ABSTRACT

Background: Sickle cell anemia is a disease that affects largely Africans and people in the tropics. It affects an average of 7.74 million and the mortality rate was 376,000 in the year 2021. Sickle cell disease was discovered in 1910 by a Famous scholar Herrick who described it as a hematological (Blood) disease and nearly three decades later, in 1949, Linus Pauling discovered the pathology of sickle cell anemia. Through molecular studies we further learned that sickle cell disease is caused by certain abnormalities in the hemoglobin of the patient, which costs millions of lives, plant products offer hope.
Aims: The objectives were to determine the plants that are in use and the consensus clinical evidence about the plants and sickle cell diseases treatment. To provide easy access to consensus evidence to busy healthcare professionals and to educate the public.
Place and Duration of Study: Department of Public Health, College of Health Science, Walden University, Minneapolis, USA, between July 2022 and October 2023.

**Corresponding author: E-mail: eahajumobi@gmail.com;*

Methodology: A systematic review supported by a community approach to intervention services and native medicine theories supported the study. Search engines were Safari, Google, Google scholar, and Firefox.
Results: Showed that while there were various approaches adopted by modern medicine to provide palliative care for persons with sickle cell diseases, which were directed at raising depleting nutrients, preventing infections and delaying the gelling point of the erythrocyte, no significant achievement has been made at reducing the disease and treating it effectively. Also, over 80% of the patients cannot afford the cost of the treatment. Thankfully, phytochemical compounds isolated from some medicinal plants- *Carica papaya*, *Piper guineense*, *Cajanus cajan*, *Zanthoxylum zanthoxyloides*, *Terminalia catappa* L, and formulations made from them such as Niprisan and Ciklavit, which have been approved for use for treating sickle cell diseases stands to be sustainable and efficacious offer hope. Outcome will bring a significant social change in local and global public health and economic activities.
Conclusion: Clinically tested phytochemical compositions of implicated plants, herbal preparations, and specific nutrients investigated in this study possess anti-sickling properties and a couple of the preparations have been approved for sickle cell disease treatment in Nigeria.

Keywords: Sickle cell; native medicine; Carica papaya and sickle cell; Zanthoxyllum macrophylla and sickle cell; Tetrapleura tetraptera and sickle cell; Terminalia catappa and sickle cell; Piper guineense and sickle cell; Parquentina nigrescens and sickle cell; Cajanus cajan and sickle cell.

ABBREVIATIONS

Term : Definition for the term
+ve : Present

1. INTRODUCTION

Sickle cell anemia is a disease that affects largely Africans, persons living in the tropical countries and along Mediterraanean. Sickle cell disease has placed a huge health burden on the populations affected. In the year 2000, an average of 5.46 million people lived with sickle cell disease and in 2021, the population increased rapidly to 7.74 million. Mortality was 376,000, involving 81,000 children under the age of five [1]. In 2021, sickle cell diseases ranked 12th among most killer diseases, which was a disproportionate increase from previous ranking of 40th position [2,1]. Sickle cell disease was discovered in 1910 by a Famous scholar Herrick who described it as a hematological (Blood) disease and nearly three decades (1949) later Linus Pauling discovered the pathology of sickle cell anemia.

Through molecular studies we further learned that sickle cell disease is caused by certain abnormalities in the hemoglobin of the patients. The normal red blood cell (erythrocyte) is usually oval in shape with biconcave structure, but prior to and when the patient is in crisis, there is a substitution of the human genetic encoding called B-globin and the B6 glutamic acid component is replaced with valine, and the result is the devastating sickle cell disease crisis because the outcome causes sickle cell hemoglobin (HbS) becomes less soluble essentially when there is no oxygen in the red blood cell, causing the sickle cell hemoglobin cell (HbS) to join together to form larger molecules and the biconcave oval shape of the erythrocyte to be lost and a new less soluble sickle shape formed. The entire process result sinto a premature breakdown of the erythrocyte, which also blocks small blood vessels and capillaries hindering the activities of the vessels and capillaries, and starving the body cells, tissues and organs of nutrients and oxygen and causing low function of the tissues, destruction and death. Some authors link sickle cell to malaria attack, which is a common disease in the tropical countries like Africa. In attempts to treat sickle cell diseases, expensive and sometimes painful treatments targeted at common symptoms of sickle cell diseases (SCD) crisis have been employed in modern medicine to bring relief to SCD patients, which is not affordable to many [3,2,1,4].

Native medicine is practiced in Asia, America, Europe, Africa and all the ends of the earth in prehistoric era until late 19th century when modern medicine emerged and about 25% of modern medicine were made from plant extracts [5]. In Africa the use of native herbs and some preparations from the herbs to treat diseases and native herbal practices are generally considered

as superstitious and those who dared to use regardless, are unsure how to use the herbs correctly to achieve goal. Some medicinal plants namely, *Carica papaya, Fagara zanoxyloides (Zanthoxyllum macrophylla), Parquentina nigrescens, Cajanus cajan and Tetrapleura tetraptera, Terminalia catappa, Piper guineense* and others were implicated to possess strong potency against the long dreaded infant and youth killer disease, sickle cell [3,2,1,4,6,7,8,9,10,11].

For a reason that sickle cell disease remains a genetic disease, which is plaquing Africans and other affected populations, causing death of majority of patients and surviving patient too expensive to treat with the existing modern medicine, which are out of reach for many, this study was found to be worthwhile. Finding within-reach, less toxic, cost effective solutions to sickle cell will save many lives and reduce the disease burden on African and populations in the tropical countries. This is a systematic review of clinical evidence from herbal plants about the efficaciousness of the herbs in controlling the life-long genetic and incurable sickle cell disease. To learn, educate and promote safe use or discourage use if clinical evidence states otherwise.

2. METHODOLOGY

The method used in performing this research is called a systematic review and the theory behind this study is traditional medicine and community approach to intervention services theories. Background is that sickle cell disease remains a disease burden in Africa and tropical countries and millions of young lives have been lost to this incurable disease and the survivors spend fortune to treat and live. And since plant remedies have been suggested to be promising for treating many diseases including metabolic syndrome and microbial, and parasitic diseases and Africans have been treating these diseases and sickle cell anemia with herbs. The time is here for scholars to separate wheat from chaff determine what is being used and if use is supported by clinical evidence or if use should be encouraged or discouraged if it is simply a myth or superstition. Because some refuse to accept use in fear of superstition. The objectives were to determine the plants that are in use and the consensus clinical evidence about the plants and sickle cell diseases treatment. Search engines such as google scholar, Safari, Google, and Firefox were used to search for peer reviewed articles about the plant used as native medicine for sickle cell treatment and existing clinical evidence. Only peer reviewed articles were selected and included in the data used for analysis. Non peer reviewed and article not available online were excluded. The results of the findings were presented, synthesized and discussed.

3. RESULTS

There are two types of sickle cell namely, sickle thalassaemia and sickle cell anemia (drepanocytosis). Sickle thalassaaemia has little or no haemoglobin, a substance in the erythrocyte that is used to distribute blood and oxygen to the body. It causes anemia, tiredness and shortness of breath and makes patient pale. Babies with genotype SS (Sickle cell disease) are usually born when both parents that have genotype AS and AS, which means that the sickle cell disease in both parents is hidden, it does not manifest. “AS” is a carrier of sickle cell but because it was not expressed (hidden) “AS” live a normal life and never suffers from the disease. But if a person with genotype “AS” marries a person with “AS”, if they did not abort or miscarry any baby, they are expected to produce one normal baby with AA genotype, two babies with AS (sickle cell carriers) and one baby with SS genotype (sickler) in every four pregnancies that they produce. Thus, a person with “AS” genotype is advised to marry AA and if ”AS” insists on marrying another “AS”, may be having three babies is most advisable. A couple with “AS” should expect to produce one sickler in four pregnancies and two sicklers in eight pregnancies [12,13,2,1].

Before now in attempts the treat or provide palliative to a sickle cell patient in crisis, modern medicine used several compounds to affect erythrocyte membrane, increase erythrocyte volume and inhibit sickling. These processes also lower the level of hemoglobin in the intracellular cell below gelling level. Most *in vivo* and *in vitro* treatment mechanism are directed at controlling molecules of haemoglobin (Hb) achievable by blood transfusion, hydroxyurea, and bone marrow transplantation, and by delay of gelling time of sickle cell hemoglobin molecule (deoxy-HbS) [2].

Substances used to manage sickle cell as palliative are antisickling and antidrepanocytary agents namely, phytomedicine (formations from physiochemical compounds, which are obtained

from medicinal plants), Niprisan (Nix-0699), a chemical compound (aromatic aldehyde), which occurs naturally in plant called 5-hydroxymethyl-2-furfural [5HMF], MX-1520: food additive, and vanillin. These compounds modify the intracellular hemoglobin of a person with sickle cell disease, and prevent sickling to occur [2].

The use of nutritional supplements such as amino acids-protein rich foods, hydroxyurea (chemotherapy), and folic acid, antimalarial drugs, and penicillin to prevent infection are common practices in managing sickle cell disease in modern medicine [2].

Also the inhalation of nitric oxide gas as hydroxyurea in destroying the sickling erythrocytes is an effective, painful and expensive practice in modern medicine. Additionally, preventing or delaying the jelling time of the erythrocyte is included in the treatment target of sickle cell diseases. Also, bone marrow transplantation is another way to treat sickle cell disease, which is very expensive [2].

3.1 Factors that Play Roles in Sickling

Though sickle cell disease until now is considered an incurable and untreatable genetic disease (diseases that occurs in nature); however, there are conditions that make the condition worse or worst. Presence of infections-malaria, cell oxidation, erythrocyte gelation and polymerization as well as certain nutrients depletion namely, Vitamins A, C and E, folic acid, and some aromatic essential amino acids (protein) aggravate sickle cell diseases crisis. These conditions can make or mare success of treatment and survival of a patient with sickle cell condition [12,13,3,2,1].

3.2 Cell Oxidation and Sickle Cell Disease Provocation

Authors have revealed that sickle cell diseases are also triggered by oxidative stress activities, which prompts the formation of reactive oxygen species (ROS), free radicals and peroxides because the amount of cell oxidation in the body out weighs the ability of the body to often neutralize ROS harmful effect. Cell oxidation weakens the cell ability to reduce perform reduction or oxidation-reduction (redox) functions. It can be caused by radiation, chain reaction of unsaturated fatty acids and many toxins that enter the body through medicines and unhealthy food. While ROS is generally harmful to the body, in case of sickle cell diseases it cause joint inflammation and erythrocytes, authors have suggested that it can be useful because it can prompt or signal the body immunity to attack and kill pathogens. At low concentration ROS damage to the cell can be repaired easily, but at high levels, it is very harmful causing organ necrosis, ATP depletion and inhibiting cell apoptotic death, and cell falling apart [2].

3.3 Gelling and Polymerization

The gelling and polymerization of sickle cell haemoglobin (HbSS) red blood cell are conditions that make sickle cell disease crisis worse or worst. Crisis usually lead to gelling and polymerization and any treatment targeted at delaying the time of the two processes, preventing or revising it is beneficial to sickle cell diseases treatment [2,14,15,16]. It is beneficial if sickle cell haemoglobin (HbSS) gelation is delayed, or prevented or reversed. HbSS is highly attractive to substances preventing and reversing sickling [2].

3.3.1 Effect of time on sickling and HbSS polymerization

In another *in vitro* research, the investigators examined the effect of phytochemical compounds on the time or duration it took for HbSS cell to polymerize. Result showed that *Carica papaya* did not delay the amount of time needed for HbSS to polymerize, however, it increased the speed of prevention of sickling and it is does-dependent. The best antisickling effect of *Carica papaya* extract was experienced at 5 mg/ml and 10 mg/ml of water extract of *Carica papaya* and that of *Fagara zanthoxyloides*, Ciklavit, *Parquentina nigrescens*, and parahydroxybenzoic acid were lower. Also, for doses of 1, 3, 5, and 10 mg/ml, papaya water extract was more effective than methanol extract of the plants studied. Low dose caused low effect and higher doses produced stronger effect.

The treatment caused nearly all the sickle cell erythrocyte to retain original shape of the red blood cell and prevented it from polymerizing or disfiguring or gelatinizing to form sickle shape. But the control group, which received no treatment excess of 80% of the erythrocyte polymerized to sickle shape [2, 1]. The outcome of this study suggested high potentiality of phytochemical compounds, and nutraceuticals of

the medicinal plants examined as well as the associated nutrients as a new hope to overcome sickle cell disease, essentially as it is non-toxic, affordable, and accessible. Authors therefore suggested further *in vivo* clinical studies with research animals like mice to determine the mechanism of action of the phytochemical compounds and the nutraceutical in controlling sickle cell disease [2,14,15,16].

3.3.2 Phytochemical compounds and antisickling function

The focus of this investigation is on phytochemical compounds with capacities to control sickle cell diseases. The result revealed that medicinal plants rich in phytochemical compounds namely, unripe *Carica papaya* fruit and dry leaves, *Piper guineense* (Igbo name, *Uziza*, Yoruba, *Iyere*, West African black pepper), *sorghum bicolor* (English name: Guinea corn, Igbo name: *Soro*, Yoruba name: *Okababa*, Hausa: *dawa*) *Eugenia caryophyllum* (English name: clove), *Pterocapus osun* (English name: Rose wood, Igbo: *Uha*, Yoruba: Gbingbin), *Parquentina nigrescent* also called *Asclepiadaceae* (Igbo name: Mgbidingbe, Yoruba: *Ewe ogbo*, Hausa: *Kwankwani*)-whole plant, *Cajanus cajan* seed extract, *Zanthoxylum zanthoxyloides* (Igbo name; *Uko/Aga*, Yoruba name: *Orin-ata*, Hausa name: *fasa-kuwari*, English name: Fagara roots (Fagara, orin-ata), aqueous and alcohol extracts of *Terminalia catappa* (Common name: tropical almond, Nigerian common name: “fruit”) leave extract and more plants have generated clinical evidence to possess the capacity to prevent and treat sickling of sickle cell diseases.

Some formulations made from some of the suggested plants namely, Niprisan-formed from *Piper guineense*, *Sorghum bicolor*, *Pterocarpus osun*, and *Eugenia caryophyllum*; Ciklavit form slated from *Cajanus cajan* (igbo name, Fio fio, Yoruba name, *Otili*, Hausa, *Waken-masar*) seed extract, and Ajawaron HF complex made from *Cissus populnea* have been clinically tested and approved for use as effective medicine for treating sickle cell diseases. Patients with sickle cell disease were found to be low in antioxidants namely, vitamins A, C and E and in cobalamin (vitamin B12), and treatments is also directed at raising those vitamins to optimum. In a study, 5 mg/ml of phytochemical medicines namely, *Parquentina nigrescens*, *Carica papaya*, *Ciklavit*, saline and parahydroxy benzoic acid was tested for antisickling potency and result showed that these compounds significantly reduced sickling effect by 2%, 0%, 5%, 15% and 50% in that order [2,1].

3.4 Vitamins and Enzymes Antioxidants

Antioxidant is a substance that prevent cells from being oxidized or from decay and the compounds that cause cell to oxidize or decay are called free radicals, a prolong excessive presence of free radicals cause the cell to decay and once that happens the next is low body immunity, which gives way to the development of metabolic syndrome diseases. Antioxidants get oxidized quickly to prevent other things (cell) around it from being oxidized. So, antioxidants reduce the cell ability to be oxidized [12,13,2,1]. Antioxidants reaction with free radicals or reactive oxygen species (ROS) forms harmless, beneficial and a stable compound, which cleans the harmful free radicals and reactive oxygen species out of the body to keep the body safe from negative or harmful effects of diseases amounting from body cell oxidation.

Vitamins as well as phytochemical compounds are antioxidants, which perform anti oxidation functions. Examples of the vitamins are Vitamins, A, beta carotene, C, and E, and phytochemical antioxidants are phenols, flavonoids, anthocyanin. Antioxidants are subjects of interest in sickle cell disease treatment because it has been discovered that most antisickling agents are high in antioxidants and oxidative stress triggers sickle cell diseases crisis [12,13,2,1]. So antioxidants will prevent the onset of crises and if crisis yet prevails, it can prevent the sickling effect. Presence of antioxidants lowers the concentration of oxidative stress enzymes. Nutrients deficiency such as folic acid, vitamins A, C, and E, and aromatic amino acid such as phenylalanine, were attributed to the stunted growth and paleness manifested in sickle cell patients [12,13,2,1].

3.5 Plants Rich in Antioxidants with Antisickling Potency

Plants isolated as having rich antioxidant capacities with strong potency against sickling are *Cajanus cajan* seed extract, *Carica papaya* leaf and unripe fruit extract, *Parquentina nigrescens* whole plant extract, and *Fagara zonthoxyloides* root extract. Although *Carica papaya* extract caused minor oxidative stress to the erythrocyte membrane, it reduced the concentration of oxidative stress and rapidly

mops up large amount of free radicals produced during SCD crisis. Use of *Carica papaya* extract for SCD treatment showed that there was reduction and outright inhibition of erythrocyte membrane lysis, which means that it also protects the erythrocyte membrane from harmful effect of osmotic pressure, reduces its fragility and rather strengthens it. Three major components of antisickling agents are antioxidant nutrients, phenolic compounds and aromatic amino acids (Phenylalanine). Antisickling agent extracted from *Zanthoxylum zanthoxyloides* was found to contain *P*-hydroxyl benzoic acid, 2-hydroxymethylbenzoic acid, vanillin acid and benzoin acid derivatives. Also contained in African Zanthoxylum zanthoxyloides is benzophenanthridine alkaloids, nitidine and 9-methpxychelerythrine. *Zanthoxylum zanthoxyloides* root extract significantly reduced the painful crisis of sickle cell patient [2].

3.6 *Carica papaya* Leaf Extract and Antisickling

Carica papaya contains 5,7-Dimethoxycoumarin, protocatechuic acid, quercetin, kempferol, *p*-coumaric acid, and trace amount of chlorogenic acid. Treatment of sickle cell in extreme lack of oxygen in the cell with 10 mg/ml and 5 mg/ml level of Carica papaya leave extract, within I hour resulted in reduction of sickle cell red blood cell (HbSS) to 0-5%. Sickle cell (SS) not treated showed excess of 80% sickle cell after the experiment. The *Carica papaya* leave extract was obtained in soxhlet extraction using five different solvents namely, water, ethyl acetate, chloroform, hexane, and butanol. The strongest antisickling effect was found with butanol extract at 10 mg/ml level, and at 5 mg/ml concentration, the highest antisickling effect occurred with ethyl acetate extract. The efficacy of the treatment was very significant. The treatment protected the erythrocyte membrane and made it more stable, it prevented HbSS (red blood cell of sickle) from hemolysis, and it prevented erythrocyte polymerization at the cell level. Treatment was dose-response so, 10 mg/ml showed higher antisickiling potency [2,1,7]. Phydroxybenzoic acid 5 ug/ml and normal saline or salt or sodium chloride (NaCL).

Also, *Carica papaya* leaf extract and three other medicinal plants such as, *Fagara zanthoxyloides* extract, *Paraquentina nigrescens* leaf extract and the seed of Cajans cajan extract showed rich antioxidant properties, which provided extra protection of the erythrocyte membrane and prevented erythrocyte hemolysis [2,1,16,7]. Also, and the phytochemical composition of the plants are similar, and are high in total phenol content, which empowers them with strong scavenging capacity against free radicals. Each plant has a stand alone capacity to scavenge free radicals and they can further exert stronger potency or synergy when two or more extract are combined together [2,1,16,7].

3.7 *Carica papaya* Unripe Fruit Extract Antisickling and Sickling Reversal

A study to determined the capacity of unripe *Carica papaya* extract to prevent and reverse sickling function the blood of sickle cell patient haemoglobin SS (HbSS) was analyzed in a sickling test using 2% of sodium metabisulphite *in vitro*. Authors determined the position of the antisickling agent as well as the minimum amount of extract required to achieve maximum prevention of sickling (antisickling). Extracts were partitioned with ethyl acetate and butanol and while water and butanol fractioning did not prevent or reverse sickling activities, ethyl acetate extract partitioning in 2% sodium metabisulphite erythrocyte of a sickle cell patient (HbSS) prevented and reversed sickle cell. 0.7 g of unripe paw paw in 1.0 ml of saline (salt solution or sodium chloride (NaCl) achieved significant sickling inhibition. Maximum (Complete) sickling inhibition was achieved with 1.0 g of unripe *Carica papaya* fruit in 1.0 ml of salt solution and reversed sickle cell erythrocyte. Conclusion: Ethyl acetate fraction of unripe *Carica papaya* extract has a capacity to prevent and reverse sickling [2,8].

It is necessary to note that various parts of *Carica papaya* plant have been suggested by clinical evident to possess healing properties, otherwise called pharmacological properties for easy digestion of protein, prevention and neutralizing of blood clots specifically achieved by papain content of the latex and unripe fruit. Also, unripe fruit and latex are affective for speedy injury, wound, ulcer, warts and boil healing. Further, *Carica papaya* twig contains annonaceous acetogenins, which is a strong chemotherapeutic agent and mechanism of chemotherapeutic function is achieved through prevention of cancer metabolic enzyme processes [8,5].

Also in a sickle cell crisis hemolysis study where 150 g of unripe *Carica papaya* fruit was incubated for 48 hours in 400 ml of water and 15

ml administered to children with sickle cell disease daily for up to seven [14] days. In this study, the quantity of potassium, sodium, bicarbonate, total and conjugated bilirubin, total protein, albumin, alanine transaminase and aspartate in the plasma of children with sickle cell disease. Result showed that metabolic acidosis, which occurred prior to and after 24 hours of treatment rose to 30 umol/litre, but dropped down to 8 umol/litre level, the amount that it was before treatment after 7 days of treatment; showing that unripe paw paw treatment significantly lowered the harmful effect of sickle cell crisis after 7 days of unripe *Carica papaya* treatment [2,10].

3.8 *Terminalia catappa L*. Family Combretaceae and Antisickling

In this research, leaves of *Terminalia catappa L*. were harvested and extracted and used for a clinical *in vitro* trial to determine its effectiveness in preventing sickling as traditionally used. Leaves were obtained from green leaves, reddish-brown leaves yet in stalk up to the tree and reddish-brown leaves, which fell down from the tree freshly. Method employed in this experiment was the capacity of the extracts to inhibit sodium metabisulphite-induced sickling of erythrocyte of sickle cell hemoglobin (HbSS), while p-hydroxybenzoic acid, 5 mg/ml and tonal salt solution of saline were used as control. Blood was collected from non-crisis sickle cell patients. Extraction of the three leaves were done with water and ethanol. Result showed trace amount of saponin in both reddish-brown leaves and significantly high saponin in the green leaves. The three leaves samples contain alkaloids, but zero amount of tannins and anthraquinones. After 90 minutes of incubation treatment, the reddish-brown freshly fallen leaves showed highest inhibition of 77% followed by reddish-brown leaves that was yet to fall and after 180 minutes of incubation treatment, slightly higher percentage, 78% of antisickling function was achieved by the fallen reddish-brown leaves [11].

This was an investigation of sickle erythrocyte's osmotic resistance to exposure to aqueous extracts of three medicinal plants namely, *Anacardium occidentale, Psidium guajava*, and *Terminalia catappa*. Methods: Authors used spectrophotometric techniques and examined the extent of erythrocyte lysis when they were suspended in saline solutions with varying concentrations and the relationship between the percentage of hemolysis in both control and test samples exhibited a sigmoidal pattern as the saline solution concentrations increased. Authors assessed membrane stability by determining the mean corpuscular fragility (MCF) index of erythrocytes incubated with aqueous concentrations of 400 and 800 mg/dL of the three plant extracts. Results: Results showed that *Psidium guajava* and *Terminalia catappa* extracts at 400 mg/dl and 800 gm/dl exhibited a protective effect on erythrocytes when exposed to osmotic stress, resulting in a decrease in MCF P values ($P < 0.05$). Conversely, 800 mg/dL of *Anacardium occidentale* induced significant destabilization of sickle erythrocytes ($P < 0.05$). Conclusion: The aqueous extracts of *Psidium guajava* and *Terminalia catappa* at both experimental concentrations demonstrated a stabilizing effect on erythrocyte membranes However, while extract of *Anacardium occidentale* achieve stabilizing effects at 400 mg/dl, at higher concentration (800 mg/dL) it did not exhibit any protective effect on the membrane [17].

3.9 Herbal Preparation Officially Approved by the Government, Which Are in Use

In Nigeria some herbal preparations have received official approval for use by Nigerian government to treat sickle cell diseases. They are Ciklavit and Nicosan.

Ciklavit: This is made from *Cajanus cajan*, essential amino acids of proteins, vitamins such as vitamin C, E, and minerals namely, zinc. *Cajanus cajan* contains important amino acids such as, cajaminose, and phenylalanine as well as hydroybenzoic acid, phenolic compounds, tannins and other amino acids. Anti gelling effects of L-Phenylalanine expressed. A sickle cell patient is always low in blood, vitamin A, C, E, and pyridoxine (B6) and minerals namely, zinc, magnesium. Also, patients experience low growth rate compared with age mates [2,1,18]. Low levels of erythrocytes, vitamins and minerals mentioned above results in massive reduction in antioxidants in the body, which causes oxidative stress. Low magnesium will mean low potassium and water and more painful bone [2,1,18].

Nicosan formerly called NPRISAN: produced from *Piper guineense*, *Sorghum bicolor*, *Pterocarpus osun*, and *Eugenia caryophyllum* extracts showed strong potency against oxidative effects and free radicals [2,1,19,18]. NIPRISAN

(Nix-0699) whether water or ethanol extract prevented 50% of erythrocyte from sickling. And the good news is there was no dehydration of red blood cells, no hemolysis and rise in the level of deformed hemoglobin, which functions are all beneficial to sickle cell disease crisis management. The use of hydroxyurea (HU) was found to the effective too. Although it has serious adverse effect like causing myelin suppression and it does not work for every patient.

Preparation called Ajawaren HF, made from *Cissus populnea L* (CPK) as a major ingredient was examined and found to be composed of phytochemical compounds namely, anthraquinone derivatives, steroidal glycosides and cardiac glycosides. Anti-sickling function was achieved by using 5 ug/ml of *p*-hydroxybenzoic acid, and control of normal saline. The objectives of this experiment were to prevent sickling activity of HbSS erythrocytes caused by metabisulphite in the red blood cell of sickle-cell patients who was in non-crisis state. The solvent of extraction were cold water and chloroform and 52.9% and 62.2% of sickling inhibition was achieved by water extract and chloroform in a duration of 180 minutes in that order. When incubated, water extract sickling prevention was highest, achieving 71.4% and p-hydroxybenzoic acid control achieved 46.0% only, after three hours of incubation [2,19,18].

3.9.1 Anti-protease and membrane stabilizing activities of extracts of F*agara zanthoxyloides, Olax subscorpioides and Tetrapleura tetraptera*

An investigation performed on *Fagara, Tetrapleura tetraptera and Olax subscorpioides* extract to determine the anti-protease and membrane stabilizing activities using spectroscopic procedure. Results showed that salt solution extracts of the plants resulted in the stability of human erythrocyte membrane, which under went hypotonic lysis and break down of cell membrane caused by heat. And as much as 84% of membrane stability was achieved by *Fagara zanthoxyloides* saline extract, 70% was achieved by *Tetrapleura tetraptera and Olax subscorpioides* 63.2%. When the plants were subjected to sodium hydroxide extraction, the plants exhibited anti-proteases function. *Fagaras zanthoxyloides* also known as *Zanthoxylum macrophylla* achieved 80% inhibition function at 1:5 dilution, *Olax subscorpioides* achieved 96% inhibition function and *Tetrapleura tetraptera* came last with 70% of antiprotenase inhibition [2,14,15,16].

In a standard chemical and chromatographic *in vitro* study, the composition of the extract of these two plants was performed to determine the proximate nutrient, mineral, amino acid, and phytochemical antioxidant content. Result showed that the plants contain Alkaloids, sponins, tannins, anthraquinone, glycosides, cyanocobalamin (B12), folic acid (B9), amino acids and minerals. Additionally, Cyanogenic glycoside was absent to suggest non-toxicity of the extract for oral use. This is a suggestion that these plants can supply a significant amount of nutrients, and phytochemical compound required to prevent sicking from occurring to a person with sickle cell disease [2,1,16].

In another study, water extract of *Fagara xanthoxyloides* roots was examined to determine the membrane stability of three human genotypes namely, HbSS, HbAS, and HbAA, a process, which is a test of the mean corpuscular fragility (MCF) of red blood cells of the genotypes. This test examined the amount of salt solution required to produce 50% of hemolysis on erythrocytes. The result showed that *Fagara xanthoxyloides* root extracted with water had effect on MCF of the three genotypes, but only the difference in (HbSS) erythrocyte membrane was significant. Percent stability when 50g/250 ml of root water extract was 10.30, 11.11, and 14.39% for HbAS, HbAA and HbSS in that order. Also, phenylalanine at 400 uM level, which is also an antisickling agent achieved the greatest membrane stabilization, of 17.85% for HbSS red blood cell and also reversed sickling effect cause by 2% sodium metabisulphite. The root extract also reversed the sickling effect caused by 2% metabisulphite [2,15].

3.9.2 Amino acids and related compounds preventing sickle cell hemoglobin (HbSS) from gelation

In another effort to find a solution to help persons with sickle cell disease, authors examined the effects of essential amino acids on HbSS gelation. Result showed that aromatic amino acids such as tryptophan, phenylalanine and some extent tyrosine increased HbSS hemoglobin solubility and significantly prevented the rate at which HbSS hemoglobin gelatinized. Certain aromatic amino acids prevented sickle cell hemoglobin (HbSS) from sickling [2,20].

3.9.3 Nutrients, plants and preparations with antisickling capacities are printed on Tables 1- 3

Table 1. Nutrients with antisickling properties

Nutrients	Antisickling Properties
Nutrients	**Properties**
Pnenylalanine	+Ve
Tryptophane	+Ve
Cyanacobolanine	+Ve
Vitamin A	+Ve
Vitamin C	+Ve
Vitamin E	+Ve

Source: [12,13,3,2,1,4]

Table 2. 17 Medicinal plants with antisickling agents

Medicinal Plants	Plant part	Antisickling Properties
Carica papaya (Paw Paw)	Leaf/unripe fruit	+Ve
Zanthophyllum macraphylla	Root/Leaf	+Ve
Cajanus cajan L. (Huth) (Pigeon pea (*Fio fio*)	Leaf/Seed	+Ve
Terminalia catappa L. (Fruit)	Reddish-brown leaves	+Ve
Piper guineense (Oziza)	Seed	+Ve
Pterocarpus osun (African Rose Wood *(Oha)*	Leaf	+Ve
Eugenia caryophyllum (Clove)	Seed	+Ve
Cissus populnea L (CPK)	Roots/Stem bark	+Ve
Olax subscorpioides	Leaf/Stem bark/fruit	+Ve
Sorghum bicolor (Sorghum)	Seed	+Ve
Tetrapleura tetraptera (*Ukpa*)	Fruit/seeds	+Ve
Paraquentina nigrescens	Leaf	+Ve
Psidium guajava (Guava)	Leaf	+Ve
Allium sativum (Garlic)	Clove	+Ve
Persia Americana (Avocado pear)	Leaf	+Ve
Anacardium occidentaale (Cashew)	Leaf	+Ve
Citrus sinensis (Orange)	Leaf/Fruit/Stem bark/peel	+Ve

Table 3. Preparations from medicinal plants

Medicinal Plants	Antisickling Properties
Preparations	**Antisickling properties**
Niprisan or Nicosan	+Ve
Ciklavit	+Ve
Ajawaren	+Ve

Table 4. Phytochemical composition of the plants

Phytochemical Compounds in the plants	Antisickling Properties
Plants	**Antisickling properties**
Alkaloids	+Ve
Saponins	+Ve
Tannins	+Ve
Flavonoids	+Ve
Cardinolids	+Ve
Steroids	+Ve
Glycosides	+Ve

+ve = Present

4. DISCUSSION

4.1 Antisickling Agents and pain Relief

Piper guineense seed antisickling capacity was attributed to its composition of capsaicin, caryophyllene, cubebin, piperine and other phytochemical compounds. Physical pain relief was found to be a major variable that *Piper guineense* controls and pain amounts for tissue damage, which patients experience during crisis [21]. It was effective for nociceptive pain experienced in peripheral nervous system as a result of mechanical, electrical, heat and chemical processes, which occur during crisis. Another type of pain experienced is called neurogenic pain that affect the entire nervous system on account of any damage to the nervous system. While *Piper guineense* and *Clove* were effective at preventing sickling and controlling pain; however, it is important to note that both cause gastric upset at high concentrations [21]. This should be considered as a side effect, which is common with modern medicine. B-Caryophyllene composed of both plants was indicated as endogenous pain antagonists and controllers [21].

4.2 Antioxidants, Oxidation and Vitamins

Antioxidants namely, Vitamin A, C, and E are beneficial for sickle cell disease control amounting from its prevention and neutralization of free radicals, which cause oxidative stress that aggravates sickle cell disease crisis [12,13,3]. Vitamin C was indicated as antisickling agent. Vitamin C prevents and heals scurvy and promotes the healing of wounds and injuries [13,3]. Vitamin A is another powerful antioxidant and yet, while vitamin C is a water-soluble vitamin, Vitamins A and E are fat-soluble vitamins. Vitamin A is essential for growth, it boosts the immune system like vitamin C and it is essential for sight. Also, like calcium, and manganese, vitamin A is needed for the formation, development of healthy bones. Additionally, quite like vitamin E vitamin A is necessary for reproduction and reproductive health and female fertility [13,3]. Vitamins A, C, and E as well as Cobalamin (vitamin B12) and folic acid (B 9) deplete in sickle cell patients essentially during and after crisis [3,2].

Cobalamin (vitamin B12) quite like folic acid, cobalamin is essential for red blood cells, nerve cells and DNA formation [13,3,2].Tocopherol (Vitamin E) is a fat soluble vitamin, which is essential for reproduction and fertility in both male and female, both prevent pregnancy abortion [13,2].

4.3 Phytochemical Compounds And Antisickling

Evidence suggests that the phytochemical agents in the medicinal plants is the vital ingredients that make up the plants' disease control potency. The phytochemical composition of the plants are Alkaloids, saponins, tannins, flavonoids, steroids (triterpenes), glycosides. These compounds play a vital role in preventing, controlling and treating oxidative stress, which clinical evidence implicated as one of the top factors that aggravates sickle diseases crisis. In other words, presence of or use of these phytochemical compounds in the body of sickle cell disease patient is one way to prevent crisis and sickling and effective management of sickle cell disease [3,2].

4.4 Herbal Preparations Approved for Treatment

There are couple of herbal preparations approved for sickle cell diseases treatment. The preparations were made from some of the medicinal plants studied and the plants derived its antisickling potency from the phytochemical properties. Also, some nutrients such as essential animo acids, vitamins and mineral usually depleted in patients during and after crisis were added to the preparations. The preparations are Ciklavit, Ajaworen and Niprisan [3,2].

4.5 Aromatic Amino Acids

Phenylalanine, vallin, tryptophan and Tyrosine were found to possess antisickling capabilities too. These aromatic compounds were isolated from the medicinal plants with antisickling capabilities, suggesting that ensuring adequate or optimum consumption of implicated aromatic amino acids is another way to treat sickle cell disease crisis [3,2].

4.6 Target for Treating Sickle Cell Diseases Crisis

Based on the outcomes of clinical evidence discussed in this research, it was established that delaying, prevention and reversal of

erythrocyte gelation, sickling and erythrocyte membrane protection and stability. Also, the prevention of occasions of suckle cell disease or conditions that triggers or aggravates the diseases progression are ways of controlling the crisis. Additionally, replenishment of depleting nutrients and treatments of damages or infections amount from the crisis, as well as pain control are ways to effectively manage sickle cell disease. The modern ways of treating sickle cell disease is less effective, it is also expensive and beyond the reach of majority of the population affected by sickle cell disease and some treatments are painful examples, chemotherapy and bone marrow transplant [12,13,2,1].

5. CONCLUSION

Although a need for further studies on the implicated plants and compounds may be necessary, there is clinical evidence that some specified nutrients, medicinal plants, phytochemical compounds and herbal preparations formulated from phytochemical compounds showed capacities to prevent, delay and reverse sickling in sickle cell patience through different mechanisms. The outcome is educational, which will be beneficial to general public, researchers, public health, health practitioners, farmers, manufacturers, investors, and policy decision makers.

6. RECOMMENDATIONS

Authors recommendations are:

1. More studies are recommended to generate more clinical evidence about the efficacies of the medicinal plants.
2. Health policy decision should make room for nutrition and herbal remedies in hospitals and clinics.
3. Healthcare professionals should create and fund nutrition and herbal units in hospitals and clinics
4. Health insurance coverage should include nutrition and herbal treatments.
5. Nutrition and herbal treatment require regulation to ensure right use and minimize misuse.
6. More experts need to be trained in nutraceutical and herbal treatment.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

Many thanks Walden University and faculty of Health Sciences for providing the platform under which this study was performed.

The selfless work of the Editor-in-Chief and editors that reviewed this manuscript and ensured that this study is presented to the public with deserved clarity was deeply appreciated.

Authors may not have come thus far without the endless and priceless prayers and support of family and friends, was beneficial in a big way. Thank you all for your self denials and sacrifices.

The providence of God in the successful accomplishment of this study was gracefully received.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Iwu MM, Igboko AO, Onwubiko H, Ndu UE. Effect of cjaminos from Canjanus cajan on gelation and oxygen affinity of sickle cell haemoglobin. Journal of Pharmacology. 1988;23(1):99-104.
2. GBD 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: A systematic analysis from the Global Burden of Disease Study 2021. The Lancet Haematology. 2023 15 June.
DOI: 10.1016/S2352-3026(23)00118-7
Accessed on July 24th, 2023.
3. Imaga NA. Phytomedicines and nutraceuticals: Alternative therapeutics for sickle cell anemia. Scientific World Journal. 2013;2013:269659.
DOI: 10.1155/2013/269659
Epub 2013 Feb 14.
PMID: 23476125;
PMCID: PMC3586489. Accessed on July 22nd 2023.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3586489
4. Acquaye CTA, Young JD, Ellory JC. Mode of transport and possible mechanism of action of L-phenylalanine benzyl ester as an anti-sicking agent. Biochimica et Biophysica Acta. 1982; 693(2): 407-416.

5. Ojewere O O. Phytochemical, proximate, mineral element composition and antimicrobial activity of some selected medicinal plant seeds.
6. Casella JF. Blood drug may painful cries in children with sickle cell diseases, study shows. Journal of the American medical Association. 2001;573:345-350.
7. Imaga NOA, Gbenle GO, Okochi VI, Akanbi SO, Edeoghon SO, Oigbochie V, Kehinde MO, Bamiro SB. Antisickling property of *Carica papaya* leaf extract. African Journal of Biochemistry Research. 2009;3(4):102-106.
8. Oduola T, Adeniyi FAA, Ogunyemi EO, Beloo IS, Idowu TO. Antisickling agent in an extract of unripe pawpaw (<I> Carica papaya </I>): Is it real? African Journal of Biochemistry. 2006; 5(20):1947-1949.
9. Sofowora EA, Isaac WA. Reversals of sickling and crenation in erythrocytes by the root extract of Fagara Xanthoxyloides. Lloxydia. 1971;383.
10. Thomas KD, Ajani B. Antisickling agent in an extract of unripe papaw fruit (*Carica papaya*). Transactions of the Royal Society of Tropical medicine and hygiene. 1987;81(3):510-511.
11. Moody JO, Segum FI, Aderounmu O, Omotade OO. Antisickling activity of *Terminalia catappa* leaves harvested at different stages of growth. Nigerian Journal of natural Products and Medicine. 2004;7:30-32.
DOI: 10.4314/njnpm.v7i1.11701
12. Ahajumobi EN, Anderson PB. *Hunteria umbellata* extract is a potent agent for effec-tive diabetes control. Asian Journal of Medicine and Health. 2022;20(8):26-36. Available:https://doi.org/10.9734/ajmah/2022/v20i830479
13. Ahajumobi EN. Nutrients, Vitamins, Mineral and Hydration for Health Restoration. I Universe, Liberty Drive Bloomington, IN 47403; 2022.
ISBN: 9781663237408
Available:https://www.iuniverse.com/en/bookstore
14. Sofowora EA, Isaac-Sodeye WA, Ogunkoya LO. Isolation and characterization of an antisickling agent from Fagara zanthoxyloides root. Lloyd. 1975;38(2):169-171.
15. Elekwa I, Monanu MO, Anosike EO. Effects of aqueous extracts of *Zanthoxylum macrophylla* roots on membrane stability of human erythrocytes of different genotypes. Biokemistri. 2005; 17(1):7-12.
16. Oyedapo OO, Famurewa AJ, Antiprotease and membrane stabilizing activities of Fagara zanthoxyloides, Olax subscorpioids and tetrapleura tertaptera. International Journal of Pharmacognosy. 1995; 130(9): 236-242.
17. Chikezie PC, Uwakwe AA. Membrane stability of sickle erythrocytes incubated in extracts of three medicinal plants: Anacardium occidentale, Psidium guajava, and Terminalia catappa. Pharmacognosy Magazine. 2011;7(26):121-5.
DOI: 10.4103/0973-1296.80669
18. Efenwonkeikie WI, Ernest AT, Toshio A. In vitro effects of NIPRISAN (Nix-0699): A naturally occurring potent antisickling agent. British Society of Haematology. 2022;118(1):337-343.
DOI: 10.1046/j.1365-2141.2002.03593.x
19. Moody JO, Ojo OO, Omotade OO, Adeyemo AA, Olumese PE, Ogundipe OO. Anti-sickling potential of a Nigerian herbal formula (Ajawaron HF) and the major plant component (Cissus populnea L. CPK). Phythotherapy Research. 2003; 17(10): 1173-1176.
20. Constance Tom Noguchi, Alan N. Inhibition of sickle hemoglobin gelation by amino acids and related compounds. Schechter Biochemistry. 1978;17(25): 5455-5459.
DOI: 10.1021/bi00618a020
21. Sunday J Ameh, Obiageri O Obodozie, Uford S Inyang, Mujitaba S Abubakar, Magaji Garba. Chapter 40 - climbing black pepper (*Piper guineense*) seeds as an antisickling remedy. Nuts and Seeds in Health and Disease Prevention, Academic Press. 2011;333-343.
ISBN 9780123756886.
DOI.10.1016/B978-0-12-375688-6.10040-4

© Copyright (2024): Author(s). The licensee is the journal publisher. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/112448