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The potential of medicinal plants in sickle cell disease control: A review

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ABSTRACT: Medicinal plants have been a source of succour in the control of many diseases in developing countries and sickle cell disease is no exception. The lower strata of the population living in developing countries rely heavily on traditional medicine due to their cultural alignment as well as their inability to afford the cost of treatment offered by orthodox medical practitioners. Myths fuelled by cultural beliefs are also issues to contend with. For example, childhood deaths within a family were always attributed to some evil forces in the traditional African setting. The advent of Western medicine changed all that when the real causes of many of such deaths became apparent.

In different parts of the world especially in Africa and Asia with high incidence of the sickle cell disease, the people have learnt to manage the problem using plants which are God's gift of nature. Crude extracts from plants have been used in treating an array of diseases since ancient times although, the bioactive components of such plants remain largely unknown. Various advances in scientific research on the use of plants and herbs brought the beneficial aspects of traditional medicine and the rationale for their uses to the limelight. This review seeks to spotlight the intervention of medicinal plants in the management of Sickle Cell Disease (SCD) by traditional healers and the underlying principles in their usage.

Keywords: Sickle cell; Herbal medicine; Medicinal plants.

Introduction

The practice of traditional medicine using medicinal plants is as old as the origin of man. This type of health care was described as Herbalism or Botanical medicine (1). The growing sophistication in lifestyle among world populations makes it imperative to refer to herbal practice as alternative or complementary medicine to appeal to a cross section of people irrespective of their cultural affiliation. These types of herbal practice that falls outside the mainstream of Western or Orthodox medicine and has remained largely unrecognized, have been described as traditional medicine, indigenous medicine or folk medicine. Two-third of the world population (mainly in the developing countries) rely entirely on such traditional medical therapies as their primary form of health care (2). A review (3) reiterated that the use of traditional medicine can not fade out in the treatment and management of an array of diseases in the African continent. This was attributed to our socio-cultural, socio-economic heritage, lack of basic health care and personnel to take charge of every nook and cranny of our rural populations.

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The bioactive ingredients that have the therapeutic activity in plants used in traditional practice are mostly unidentified and traditional healers believe in the holistic nature of their treatment. Substances found in medicinal plants, containing the healing property of plants (4) is known as the active principle. It differs from plant to plant and examples of active principles include: anthraquinones, flavonoids, glycosides, saponins, tannins etc. Plants also contain other compounds such as morphine, atropine, codeine, steroids, lactones and volatile oils, which possess medical values for the treatment of different diseases (5). In recent years, these active principles have been extracted and used in different forms such as infusions, syrups, concoctions, decoctions, infused oils, essential oils, ointments and creams(6). Since most plants have medicinal properties, it is of utmost importance that their efficacy and toxicity risks are evaluated (1).

Sickle cell disease is known to be one of the diseases ravaging most world populations cutting across nations and ethnic divide. The disease was first identified by a hospital intern when a black medical student complained of shortness of breath, heart palpitations, abdominal pains, aches and pains in the muscle. The shape of the red blood cells was then used to describe his observations (7). According to reports, Africa is believed to be the origin of sickle cell disease, and those afflicted with the disease are estimated at 200,000 per year (8). The recurrent and painful symptoms experienced during crises by sickle cell patients are known by various names in different parts of the world with high incidence of the disease.

Due to the challenges faced by scientists in developing countries, so many sources of constituents capable of ameliorating the sickle cell crises have been investigated with a view to contributing to the search for substances that would be effective in solving the sickle cell disease problem. Consequent upon this, anti sickling effects of different substances have been investigated. Dried fish (*Tilapia*) and dried prawns (*Astacus* red) extracts were established to have the ability to inhibit polymerization of sickle cell hemoglobin (HbS), improve the $\text{Fe}^{2+}/\text{Fe}^{3+}$ status and lower the activity of lactate dehydrogenase (LDH) in the blood plasma. LDH is a sensitive indicator of hemolysis and its level in sickle cell blood, determines the severity of crises (9). Hydroxyurea, erythropoietin and tucaresol preparations have been found to reduce LDH activity and bilirubin level in serum, as well as increase the level of fetal hemoglobin (HbF) (10, 11). There have also been reports on effective management of SCD patients during pregnancy (12, 13).

In Nigeria and most parts of developing countries, medicinal plants have been used in the treatment of painful crises associated with sickle cell disease (SCD) 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. One of our primary sources of information on the use of medicinal plants is local herb sellers, unorthodox doctors and those whose knowledge of herbs were passed to them by their ancestors. Scientific evaluations are then undertaken to authenticate the traditional use of the plants.

The Problem

Sickle cell disease is caused by the substitution of glutamic acid with valine at the sixth position of the beta-globin chain of hemoglobin S (HbS) (14) and different amino-acids can be substituted at the same time (15). The variants of sickle cell disease include those that produce prominent clinical manifestations as seen in sickle cell anemia HbSS, sickle cell HbC disease, sickle cell α -thalassemia, while sickle cell trait (HbAS), which has never been considered a disease, has one abnormal gene (16). The deficiency caused by abnormal hemoglobin like HbS, HbC, Hb α -thalassemia and glucose-6-phosphate are now known.

Under hypoxic conditions, deoxy-HbS molecules polymerise, forming rigid, sickled cells.

This in turn causes the deformation of the normal disc biconcave RBC (14). Due to polymerization of the sickled cells, the red cell membrane loses its functional abilities which results in loss of K^+ and water and a corresponding gain of Na^+ . Increased intracellular free Ca^{2+} occurs during sickling (17), resulting in a loss of K^+ with accompanying movements of Cl^- and water. Small blood vessels are blocked by the clumping of sickled RBCs, preventing blood supply to various organs. Deoxygenation in tissue capillaries causes damage to its endothelium, leading to exudation of plasma into the surrounding soft tissue. This is characteristic of the soft tissue swelling seen in most sickle cell disease patients (18).

The RBC membrane's integrity is maintained by hydration and if the membrane becomes dehydrated, this impacts on its deformity which may lead to sickling. Nitric oxide is also believed to play a part in sickle cell disease. It was reported that it may be beneficial to SCD patients if endogenous NO production is stepped up, amplifying NO response or decreasing its destruction (19). This is to prevent Hb released as a result of haemolysis consuming NO and triggering a cascade of events that ultimately inhibit blood flow.

Clinical Manifestations

The phenotypic expression of sickle cell anemia varies greatly among patients and longitudinally in the same patients (20). Clinical manifestations of sickle cell disease are diverse and varied and fall into three major categories: anemia, pain related issues and organ failure. Blocked blood vessels and damaged organs can cause acute painful episodes or “crises”. Sickle cell crises may be caused by blood vessel occlusion, triggered by membrane deformation (21). SCD patients suffer from a variety of ailments which includes acute chest syndrome (ACS) which is one of the reasons for hospital admissions (22), stroke (23), and acute splenic sequestration (24, 25). Other clinical manifestations of this condition are hyposthenuria, priapism, vascular necrosis, proliferative retinopathy, aplastic crises, cholelithiasis, delayed growth and sexual maturation, chronic pulmonary disease and chronic nephropathy (26).

However all these clinical features of the sickle cell disease do not appear until after the first sixth months of life, at which time most of the HbF has been replaced by HbS.

Orthodox Lines Of Treatment

Early researches(27) stated that in treatment of SCD, it is required that one focuses on the ways of inhibiting sickle cell haemoglobin polymerisation, prevention or repair of red cell dehydration and interrupting the interaction of sickle cells with the endothelium.

Some of the orthodox modes of treatment include induction of fetal hemoglobin (HbF) using Hydroxyurea (HU), Butyrate or its derivatives, oral administration of Clotrimazole which is a potent Gardos channel inhibitor, Blood Transfusion and Hematopoietic Cell Transplantation (HCT).

The induction of fetal hemoglobin has been the most promising of all the lines of orthodox treatment used in the management of sickle cell disease (28, 29). Fetal hemoglobin is believed to interfere with the polymerized globin chains whose interaction with each other results in rigidity of the cells. In randomized adult patients’ trials, treatment of the patients with HU reduced the acute chest syndrome and the need for blood transfusions, also reducing the painful crises by as much as 50% (30). Successful use of HU was also reported (31) in children.

However, side effects or poor drug efficacy of some of these agents poses problems for many patients (14). HU was initially developed because of its ability to increase fetal haemoglobin production (a known inhibitor of sickle cell polymerization). Butyrate and Decitabine are some drugs evaluated for their ability to increase foetal haemoglobin concentration (32, 33).

Drugs to prevent dehydration of the sickle RBCs have also been studied including Clotrimazole, Mg and ICA-17043 ‘quintiles’. Newer applications to preventive therapy include cellular rehydration with agents that inhibit the Gardos channel or the KCL co-transport channel ((34). A new Gardos inhibitor ICA-17043 (35) which is much more potent and selective than Clotrimazole was reported. The oral rehydration therapy has recorded great success in the management of sickle cell disease. In one of our laboratory experiments on anti-sickling and de-sickling properties of medicinal plants we came across a student who had no semblance of a sickle cell patient and she attested to having fewer crises. I wanted to know her secret for experiencing fewer crises like once a year or non at all. She simply told me that she takes her folic acid and a lot of water on a daily basis. Unfortunately this student did not die from the disease but from a motor accident. This buttresses the efficacy of oral rehydration therapy.

The anti-sickling properties of certain amino acids such as phenylalanine, alanine, lysine, arginine etc have also been reported (36). The modulation of the activities of the three membrane-based ATPases (Na^+ , K^+ , Ca^{2+} ATPases) were shown to be significantly lowered in HbSS erythrocytes, while Mg^{2+} ATPases was significantly higher than for HbAA erythrocytes (37).

The role of Ca^{2+} in preserving the low permeability of the red cell to the K^+ and Na^+ , and thereby maintaining the normal low rate of cation leakage from the cell had been reported (38). Indeed it had been suggested that sickling of red cells could be reversed if excess Ca^{2+} in the red cells is pumped out (39). Deoxygenation increases membrane permeability to Mg^{2+} leading to a net loss of intracellular Mg^{2+} .

Results obtained from a study (40) indicated that the Thiocyanate, Hydroxyurea, and Tellurite are potent antisickling agents as evident from their remarkable ability to inhibit sickling of deoxygenated sickle red blood cells *in vitro*. Thiocyanate and hydroxyurea increased red cell life span *in vitro* while Tellurite caused red blood cell osmotic fragility and may induce haemolytic anaemia in sickle cell patients. Thiocyanate and hydroxyurea interact directly with sickle red blood cell as indicated by increased solubility and oxygen

affinity of sickle red blood cell in the presence of the two drugs. Thiocyanate was adjudged to be the most efficient out of the three drugs tested followed by Tellurite.

The use of blood transfusion has helped in sickle cell disease management but with some complications. Complications arise from hyperhemolysis that occur during blood transfusion (41) and it is believed that the patient's cells and transfused cells become destroyed by macrophages.

Bone marrow transplantation in children has recorded good curative results in some patients (42). Nitric oxide, a potent vasodilator has been evaluated for its anti-sickling properties (43). Other orthodox lines of treatments being pursued include anti-adhesion and anti-oxidative therapies (44).

Potentials Of Medicinal Plants

In developing countries where the use of herbal remedies is at its peak, the potential benefits of using medicinal plants in the management of sickle cell disease should not be under estimated. The holistic use of plants in health care affords the benefit of maximizing all the essential ingredients that nature has endowed to humanity. Some of these plants have antioxidant; anti-inflammatory, antimicrobial and anti-adhesion properties while others may be involved in boosting the immune system, working as analgesic, aphrodisiac or aiding general metabolism. The cocktail encompassing all these properties may result in a healthy man living till a mature old age.

The health care cost of the management of sickle cell disease (SCD) patients is disproportionately high compared to the number of people afflicted by the disease. The common people living in the villages are mostly peasant farmers who cannot afford the high cost of treatment by Orthodox doctors (45). Considering all genetic disorders to which man is known to be liable, there is probably no other that presents a collection of problems and challenges quite comparable to SCD and related disorders. Due to the debilitating effect and cost of managing the SCD, research has been on-going to determine the efficacy of the use of medicinal plants to tackle the multiple challenges presented in sickle cell disease.

The traditional healers without any scientific background have made use of nature's abundant resources to manage sickle cell disease with a great degree of success over time. It was not until the advances in science revealed the underlying mechanisms of the drugs used in orthodox medicine for the management of sickle cell disease that researchers started putting pieces of information together to identify the therapeutic properties of plants hitherto used by traditional medicine practitioners to treat sickle cell patients. Since then, a lot of information has flooded the literature database on how these plants help to alleviate the problem of sickle cell patients.

The use of phytomaterials such as *Piper guineensis*, *Pterocarpa osun*, *Eugenia caryophyllala* and *Sorghum bicolor* extracts for the treatment of sickle cell disease was reported by (46).

The extract of *Pterocarpus santalinoides* and *Aloe vera* was reported to increase the gelling time of sickle cell blood and inhibits sickling in vitro. This indicates that such plants may indeed have a great potential in the management of sickle cell disorder (47). The reversal of sickling by root extracts of *Fagara zanthoxyloides* has also been reported (48).

Terminalia catappa could be an effective antisickling agent inhibiting osmotically induced haemolysis of human erythrocytes (49) in a dose dependent basis. The use of *Scoparia dulcis* (50, 51) in the management of sickle cell disease by one woman for over two decades and the efficacy of the plant in the management of sickle cell disease was speculated. They therefore, used *Trypanosome brucei* to investigate the effect of the plant on hematological and biochemical indices due to lack of animal models for assessing the effectiveness of the plant extract in sickle cell disease monitoring.

Thirteen Congolese plants (52) were screened for antidrepanocytary activity (anti-sickle cell anaemia) and only twelve of them were reported to possess such properties. These plants are *Alchornea cordifolia*, *Aframomum albo violaceum*, *Annona senegalensis*, *Cymbopogon densiflorus*, *Bridelia ferruginea*, *Ceiba pentandra*, *Morinda lucida*, *Hymenocardia acida*, *Coleus kilimandcharis*, *Dacryodes edulis*, *Caloncoba welwithsii*, and *Vigna unguiculata*.

The role of crude aqueous extract of *Zanthoxylum macrophylla* roots as an anti-sickling agent was also highlighted (53) and 2-hydroxybenzoic acid was isolated and identified as the anti-sickling agent obtained from the root of this plant.

Garcinia kola is a popular seed consumed by the locals in Nigeria and it is also known as 'bitter kola'. It has been speculated to be effective in the management of sickle cell disease. An investigation of the aqueous extracts of *Garcinia kola* (37) to confirm the above claim indicated that it was higher and more effective on membrane stabilization than phenylalanine.

The membrane stabilization activity of aqueous extract of *Zanthoxylum macrophyllum* roots (53) was observed to be lower than phenylalanine which differs from the report on *Garcinia kola*. *Senna alata* and *Senna podocarpa* membrane stabilizing properties (54) had been identified but the stabilizing activity was found to be higher in *Senna alata*. The pharmacological agents that alter membrane stability could be applied in the control of sickling process of erythrocytes, a major physiological manifestation of the sickle cell disease (55).

Several reports indicate that the membranes of human erythrocytes from HbAA, HbAS and HbSS blood types have varying stability as determined from the mean corpuscular fragility (37), therefore plant extracts that can positively affect the red cell membrane would be useful in sickle cell disease management. Furthermore, it has been suggested (56), that the extract of the seed of the *Cajanus cajan* was effective in restoring normal morphology of erythrocytes from blood samples of patients affected by sickle cell anemia. Thus, Aged garlic could be useful in sickle cell management (57, 58) because it has been found to suppress hemolysis and prevented reduced membrane deformability.

Some researchers (59, 60) investigated the usefulness of *Carica papaya* as an antisickling and found that indeed, the unripe *Carica papaya* has antisickling properties. Some herbal cocktails have been produced and tested for their ability to intervene in sickle cell crises. The drug Nicosan previously NIPRISAN (Nix-0699), which is a product of the extracts of four different plants, (*Piper guineenses* seeds, *Pterocarpus osun* stem, *Eugenia caryophyllum* fruit, and *Sorghum bicolor* leaves) were shown to possess anti-sickling properties (61). Clinical trials of Nix-0699 showed that the drug significantly reduced the number of painful episodes in SCD patients.

Nix-0699 was able to improve the survival rates of transgenic cell mice under acute severe hypoxic conditions (14).

The extracts of the roots of *Cissus populnea* L. CPK (a major constituent of a herbal formula Ajawaron HF used in the management of sickle cell disease in south west of Nigeria), has been examined for its antisickling properties and was found to be efficacious as an anti-sickling agent.

The African herbal formula (62), as a hematinic, increases the hemoglobin, packed cell volume and white blood cell levels. This preparation which has been on sale in Nigerian markets under a new name (Jobelyn or Jubi), helps in bolstering the hemoglobin, pack cell volume and white blood cells whose deficiencies are among the hallmarks of the disease. There are some other drugs prepared from medicinal plants in the market today under various names. The most prominent and widely used of them all is Ciklavit developed by Prof G Ekeke after eighteen years of intensive research in collaboration with Neimeth Pharmaceuticals, Lagos, Nigeria.

All these claims on the efficacy of medicinal plants in the management of sickle cell however have their setbacks. *Adansonia digitata* L (*Bambacacae*) which was reported to be effective in treating sickle cell anemia patients was not active as an anti sickling agent in vitro (63). We observed in our laboratory that some of the plants typed for anti-sickling activity, did not possess such activity but rather boosted the level of red blood cell and white blood cell count and had de-sickling activity. Some of these plants may not be direct anti-sickling agents but may indirectly contribute to ameliorate so many multiple factors inherent in sickle cell disease condition. The resultant effect of the actions of these plants is the ability to manage sickle cell disease patients.

BIOACTIVE CONSTITUENTS OF MEDICINAL PLANTS USED IN SICKLE CELL DISEASE MANAGEMENT.

Not much in-depth study has been undertaken on the bioactive constituents of medicinal plants generally due to lack of sophistication in medicinal plant research in most of the places known to have high incidence of the disease. The result is that most scientists from these areas are hindered in their quest to identify the active components of such medicinal plants which has shown great potential in sickle cell disease management.

Phytochemical examination of the extract of herbal formula Ajawaron whose main constituents are roots of *Cissus populnea* L. CPK was found to contain anthraquinones derivatives, steroidal glycosides and cardiac glycosides. Alkaloids and tannins were completely absent in CPK extracts (64). Furanoditerpene constituent isolated from *Sphenocentrum jollyanun* was used for the treatment of inflammation related diseases of which sickle cell is one of them (64).

A compound isolated from *Khaya senegalensis* possessing antisickling activity was identified as rearranged limonoid. (65). *Scoparia dulcis* has been reported to be rich in flavonoids and terpenes (66, 67,

68, 69). 5-hydroxymethyl-2-furfural (5HMF), a naturally occurring aromatic aldehyde inhibits red cell sickling by allosterically shifting oxygen equilibrium curves towards the left (70). Other bioactive compounds isolated include epigallocatechin gallate from green tea (71), 2-dihydroxybenzoic acid from *Zanthoxylum macrophylla* (53). The Nigerian *Zanthoxylum* has been extensively studied (72). The bioactive compounds responsible for anti-sickling properties were identified as vanillic acid, p-hydroxy benzoic acid and p-fluoro benzoic acid. They were found to be active at low concentrations and the latter was the most active.

Isomeric divanilloylquinic acids isolated and identified from *Fagara zanthoxyloides* obtained from Burkina Faso (73), was suggested to play a role in sickle cell disease management. In addition, another bioactive compound (2-dihydroxymethyl benzoic acid) isolated and characterized from *Fagara zanthoxyloides* was found to be the anti-sickling agent (74).

ALTERNATIVE THERAPY IN THE MANAGEMENT OF SICKLE CELL DISEASE (SCD) IN THE 21st CENTURY

THE ROLE OF ANTI-OXIDANTS.

Some researchers have argued in favor of nutrition in the management of sickle cell disease. Preliminary studies (75) to evaluate the effect of aged garlic extract on SCD patients showed a reduction in aggregates that adhere to red blood cells and damage it without significant changes to RBC, hemoglobin, and reticulocyte count. Epigallocatechin gallate from green tea has been shown to reduce sickling of RBC by 30%. Many investigations have been carried out on the role of some dietary supplements, such as Thiocyanate (76, 45) in the management of sickle cell disease.

Oxidative damage to cells is believed to be responsible for activation of KCL-cotransport in sickled erythrocytes (77). The sickle cell erythrocytes are fragile and dehydrated and it is important that minerals and anti-oxidants are constantly supplied to maintain hydration and membrane integrity. Therefore many tropical plants have been investigated for their micronutrients and anti-oxidative properties. Some of the plants examined so far include *M. charantia* (78), *Cymbropogon citratus* and *Camellia sinensis*(79), *Scoparia dulcis* (80), Aged garlic(57) and *Picrorhiza kurroa* (81).

TRANSGENIC ANIMALS IN SICKLE CELL MEDICINAL PLANTS RESEARCH

Further studies with transgenic (Tg) sickle cell mice showed that orally administered 5HMF inhibited the formation of sickle cells and significantly prolonged survival time under severe hypoxia, compared with untreated mice (61). A vanillin pro-drug, MX-1520, which is biotransformed to vanillin in vivo, reduced the percentage of sickle cells under hypoxia in transgenic sickle mice. This demonstrates the potential of MX-1520 to be a new and safe anti-sickling agent for patients with SCD (82).

The use of transgenic animals to effectively probe the usefulness of some of the plants with probable lead components in alleviating sickle cell crises has not been extensively undertaken by researchers in developing countries. Lack of adequate laboratory facilities and funding has hindered progress in this direction.

With the vast natural resources available in these regions, provision of adequate funds and well equipped modern laboratories would go a long way towards actualizing the dream of these Scientists to solve their localised health problems without recourse to areas where some of these diseases are foreign.

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