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Review Article

Evaluation of Traditional Medicine to Cure Sickle Cell Anaemia: A Review

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Abstract

According to this assessment, medicinal plants have shown to be an invaluable tool in the treatment of a wide range of illnesses in underdeveloped nations, including sickle cell disease. Due to cultural choices and the high expense of conventional treatment, many people in both industrialised and developing nations rely significantly on traditional medicine. The bioactive compounds responsible for the therapeutic effects of these plants are often unidentified, and traditional healers emphasise a holistic approach in their treatments. These therapeutic compounds are referred to as the "active principles" of the plants. In the context of sickle cell anaemia, herbal medicine plays a crucial role. Research indicates that while the gene causing the disease is dominant and highly expressive, males are more affected than females, whereas females usually act as carriers because the gene is recessive. Numerous plants with immunomodulatory effects have been reported in the literature, and some of these have been validated through the use of contemporary scientific techniques. The usefulness of several phytomaterials in treating sickle cell disease has been documented. These include of Zanthoxylum Chalybeum, Cajanus cajan, Garcinia kola Heckel, Carica papaya, Scoparia dulcis, etc. and *Aloe vera* can reduce sickling in vitro and lengthen the gelling period of sickle cell blood. These findings indicated that these plants have a great deal of possibilities for treating sickle cell diseases.

Keywords: Sickle cell disorder, traditional medicines, medicinal plants, anti-sickling agents, Zanthoxylum chalybeum; Cajanus cajan; Carica papaya

History

Sickle cell was first reported by James B Herrick [1] (United States) in red blood cells year 1910. The disease was named sickle-cell anaemia by Verne Mason in 1922. Pauling [2] described sickle cell anaemia as a molecular disease and showed that it had different electrophoretic properties

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from normal human haemoglobin. This was the first time a genetic disease was linked to a mutation of a specific protein, a milestone in the history of molecular biology, and it was published in their paper Sickle Cell Anemia, a Molecular Disease. Subsequently, this change in electrophoretic mobility was found to be due to the substitution of the glutamic acid residue at position 6 by valine in the beta chain of the haemoglobin molecule (,6 Glu→Val) [3]. The first case of sickle cell anaemia in an Indian of 22 years of age, born to Indian parents in Durban, was reported by Berk and Bull [4] from Cape Town. Sickle cell trait in South India was first described by Lehmann and Cutbush [5] among the original tribes of the Nilgiri Hills. In the same year, Dunlop and Mazumder [6] reported five cases of sickle cell trait and three presumptive cases of sickle cell anaemia among the tea garden labourers of Upper Assam, originating from the tribal population of Orissa and Bihar. The HbS gene is widespread among many tribal and non-tribal populations of India.

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), and different amino acids can be substituted at the same time. 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.[7] The deficiency caused by abnormal hemoglobin like HbS, HbC, Hb α-thalassemia and glucose-6-phosphate, is 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. Due to polymerisation 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 Ca2+ occurs during sickling, resulting in a loss of K+ with accompanying movements of Cl- and water.[8] 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.[8]

Clinical Manifestations

The phenotypic expression of sickle cell anemia varies greatly among patients and longitudinally in the same patients. 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. SCD patients suffer from a variety of ailments which including acute chest syndrome (ACS), which is one of the reasons for hospital admissions, stroke, and acute splenic sequestration. 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.[9]

Introduction

Hemoglobin is the main component of red blood cells (RBC), and is responsible for transporting oxygen throughout the body. Hemoglobin A (Hb A), the most common form, is composed of two alpha (α) and two beta (β) globin chains. Normal RBCs are mainly composed of Hb A and have a biconcave shape, which allows them to pass through small blood vessels. Sickle cell anemia is a genetic disorder of hemoglobin. The mutation triggers a single amino acid substitution of glutamic acid for valine at the sixth position on the β-globin chain to generate hemoglobin S (Hb S), which polymerizes in hypoxic conditions to give rise to abnormal sickle-shaped RBC [10]. The disease is inherited in an autosomal recessive way. Homozygous patients are often affected by hypoxia, vaso-occlusive pain crises and strokes

because of the aggregation of sickled RBC in the microcirculation. Approximately 300,000 newborns are affected each year, and 5% of the global population is healthy carriers; this can reach up to 25% in some African areas exposed to malaria [12]. Moreover, the total number of patients affected by sickle cell disease is expected to increase due to the remarkable level of protection that the sickle cell provides against malaria [11]. Indeed, people affected by sickle cell anemia in malaria-endemic areas seem to have a significantly increased lifespan, which leads to positive natural selection. Due to slave trading and migration, sickle cell disease has spread to most developed countries, and in these malaria-free countries, the life expectancy for patients with sickle cell disease is reduced by approximately 30 years [11]. As it is a genetic disease, there is no pharmacological cure for sickle cell anemia, however, various techniques are currently used to treat the symptoms, including blood transfusion and hydroxyurea. This chemotherapeutic drug is known to decrease the occurrence of vaso-occlusive crises notably by stimulating the production of fetal hemoglobin (Hb F) in RBC; however, the detailed biological mechanism has not yet been elucidated [13]. Treatment with hydroxyurea also has several disadvantages, including risks factors associated with its long-term usage; moreover, it is an expensive treatment, especially for patients from less developed countries.

This study aims to promote the use of medicinal plants by traditional healers in the treatment of sickle cell disease (SCD) and the guiding ideas behind their application. The ability of several drugs to prevent sickling has been studied. Numerous plants have been mentioned in literature as having immunomodulatory effects. This Article includes a review of **Zanthoxylum Chalybeum, Cajanus cajan, Garcinia kola Heckel, Carica papaya, Scoparia dulcis, etc.**

1. Zanthoxylum Chalybeum:

Zanthoxylum chalybeum Engl. is a traditional medicinal plant, which is native to Eastern and Southern Africa. Commonly known as the 'Knob wood', it has been used for centuries by several traditional healers in Kenya, Tanzania, Uganda, Zambia and Zimbabwe. The species is very well known to local communities by its common names such as 'Kundanyoka' (Shona), 'Mjafari' (Swahili) and 'Ntaleyedungu' (Uganda), and it grows naturally in the tropics and subtropics. *Zanthoxylum chalybeum* has been previously studied for its pharmacological properties. Research has shown tremendous results on the antibacterial, antifungal, antiplasmodial, antidiabetic, anticancer and antisickling properties of Zanthoxylum *chalybeum* [14-19].

Analysis of active chemical compounds of Zanthoxylum *chalybeum* has shown the presence of reducing sugars, alkaloids, anthracenosides, coumarine derivatives, flavonoids, steroid glycosides, triterpenes, anthocyanocides, saponins and cardiac glycosides [20]. In Uganda, Kenya and Tanzania, Zanthoxylum *chalybeum* was most frequently used ethnobotanically to treat malaria. The most widely used plant parts were the roots (23), followed by the stem (12), leaves (8) and lastly berries (3).

2. **Cajanus cajan (L.) Huth** is the scientific name for pigeon pea,, a vital grain legume in semi-arid tropics has been reported for its traditional use for the treatment of sickling disorders [21]. In the western region of Cameroon, such as "Banguo, Bafoussan, Foumban and Bandjourn, traditional healers use the seeds of Cajanus cajan for the treatment of sickle cell anemia" [22]. Among the "Hausa, Efik and Idoma ethnic groups of Nigeria, Cajanus cajan is used as the major

herbal medicine for the treatment of sickle cell disease" [23]. In the Southwestern region of Nigeria, specifically, "Osun, Ondo and Oyo, traditional healers utilize the aqueous extract of the seeds of Cajanus cajan for the treatment of sickle cell disease" [21, 24].

In the south-south region of Nigeria, specifically Edo state, [21] reported that Cajanus cajan is utilized for the treatment of sickle cell disease. Furthermore, in the southeastern part of Nigeria, especially among the Nsukka community, traditional healers use the alcoholic extract of Cajanus cajan seeds for the treatment of sickle cell patients commonly known as "Ogbanje"[21]. While the plant has been studied for various properties, including anti-inflammatory, anti-bacterial, anti-carcinogenic, anti-diabetic, anthelmintic, hypocholesterolemic, neuroactive, analgesic, and anti-oxidative effects, there is limited information on its therapeutic potential for sickle cell beta thalassemia [25]. This study aims to verify the link between the traditional use of two varieties of Cajanus cajan (white and brown) and their pharmacological activities for the treatment of sickle cell beta thalassemia, intending to determine which variety exhibits stronger therapeutic properties.

3. *Garcinia kola Heckel*

Garcinia kola Heckel belongs to the family Guttiferae. It is commonly known as bitter kola (English). Garcinia kola has been a subject of intense scientific investigations. Garcinia kola has been proven to exhibit pharmacological uses in treating coughs, throat infections, bronchitis, hepatitis, and liver disorders [26].

It served as a bitter stimulant and as a snake repellent when they are placed round the compound [27]. Other medicinal uses of this plant include purgative, antiparasitic and antimicrobial. This plant has shown bronchodilator effect [28], anti-inflammatory, antibacterial and antiviral properties [29-30], antihepatotoxic effect [31] and antioxidant activity . In south west Nigeria, G. kola is one of the constituents of a traditional recipe that is used in the management of sickle cell disease (SCD) [32].

4. Carica papaya:

The papaya, or Carica papaya, is a small, tropical evergreen tree best known for its sweet, melon-like fruit. The vitamin C content increases as the maturity progresses. Its carbohydrate content is mainly in invert sugar, which is a form of predigested food [33]. Its main medicinal use is as a digestive agent; it is prescribed for people who have difficulty digesting protein and is used to break up blood clots after surgery, which is due to the presence of the enzyme papain in the plant's latex. The latex from the trunk of the tree is also applied externally to speed the healing of wounds, ulcers, boils, and warts. The seed is used to expel

worms, and the flower may be taken in an infusion to induce menstruation[33-34].

It has been documented that black seeds of papaya are highly beneficial in the treatment of cirrhosis of the liver caused by alcoholism, malnutrition, etc[33]. Ripe papaya has also been reported to be highly valuable in the enlargement of the spleen [33]. Aqueous extract of unripe Carica papaya has been documented to possess antisickling properties. Oduola et al [35] confirmed this property and established the minimum concentration of the unripe Carica papaya that achieved maximum antisickling to be 1g/ml in physiological saline. Solvent partitioning revealed that the antisickling agent resides in the ethyl acetate fraction of the extract [35]. Nontoxic effect of ingestion of aqueous extract of unripe Carica papaya on liver functions in sickle cell patients of different age groups had also been documented [36]. The effect of ingestion of aqueous extract of unripe Carica papaya on kidney function in sickle cell patients was also reported to be normal[37]. Hematological parameter was also established to be normal in sickle patients who ingested unripe Carica papaya aqueous extract for 6 months[38].

5. Scoparia dulcis:

Scoparia dulcis, also known as sweet broom weed or licorice weed, is a tropical herb with a long history in traditional medicine. Originally from the Americas, it is now found pantropically and is used to treat a wide array of ailments, with modern research confirming many of its pharmacological properties.

Ethnomedicinally, Scoparia dulcis is used to manage sickle cell disease in Nigeria [39], used for anaemia, burns, headache in Nicaragua [40], used to treat diabetes in India and hypertension in Taiwan [41] and also for bronchitis [42]. Sickling decreases the RBC's flexibility and results in risk of various complications such as chronic renal failure [43], retinopathy [44], pulmonary hypertension [45], chronic pain [46], ischemia [47], stroke [48], priapism and infarction of the penis [49].

Causes, incidence, and risk factors

Sickle cell anaemia is caused by an abnormal type of haemoglobin called haemoglobin S. Haemoglobin is a protein inside red blood cells that carries oxygen. Haemoglobin S changes the shape of red blood cells, especially when the cells are exposed to low oxygen levels. The red blood cells become shaped like crescents or sickles. The fragile, sickle-shaped cells deliver less oxygen to the body's tissues. They can also get stuck more easily in small blood vessels and break into pieces that interrupt healthy blood flow.[50] Sickle cell anaemia is inherited from both parents. If you inherit the haemoglobin S gene from one parent and normal haemoglobin (A) from your other parent, you will have sickle cell trait. People with sickle cell trait do not have the symptoms of sickle cell anaemia. Sickle cell disease is much more common in people of African and Mediterranean

descent. It is also seen in people from South and Central America, the Caribbean, and the Middle East.[51]

Symptoms: [52]

Symptoms usually don't occur until after age 4 months.

Common symptoms include:

- Bone pain
- Breathlessness
- Fatigue
- Fever
- Attacks of abdominal pain
- Rapid heart rate
- Ulcers on the lower legs (in adolescents and adults)

Signs and tests:[52]

Hemoglobin Electrophoresis (also known as HPLC/Capillary Electrophoresis) is used to detect aberrant hemoglobin, the Complete Blood Count (CBC) examines the quantities of red blood cells and hemoglobin, and genetic testing determines the precise gene mutation causing the illness. While diagnostics like MRI can track issues, newborn screening is essential for early diagnosis.

Complications:

- Acute chest syndrome
- Anaemia
- Blindness/vision impairment
- Brain and nervous system (neurologic) symptoms and stroke
- Death
- Disease of many body systems (kidney, liver, lung)
- Drug (narcotic) abuse

Prevention:

Sickle cell anemia can only occur when two people who carry sickle cell trait have a child together. Genetic counselling is recommended for all carriers of sickle cell trait. About 1 in 12 African Americans has sickle cell trait.[53] If you have sickle cell anemia, you can prevent the change in red blood cell shape by:

- Getting enough fluids
- Getting enough oxygen
- Quickly treating infections

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 underestimated. The holistic use of plants in health care affords the benefit of maximising all the essential ingredients that nature has endowed 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 analgesics, aphrodisiacs or aiding general metabolism. The cocktail encompassing all these properties may result in a healthy man living till a mature old age.

The use of *Scoparia dulcis* 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. Crude aqueous extract of *Zanthoxylum macrophylla* roots as an anti-sickling agent was also highlighted, 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* to confirm the above claim indicated that it was higher and more effective on membrane stabilisation than phenylalanine.[54] Furthermore, it has been suggested 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 anaemia.

Conclusion

Promising complementary methods for the treatment of sickle cell disease (SCD) are provided by herbal medicine. Numerous plant extracts, including those from the Zanthoxylum family, Carica papaya, Garcinia kola Heckel,

Scoparia dulcis, and Cajanus cajan, have shown antioxidant, anti-sickling, and pain-relieving qualities that may lessen symptoms and enhance patients' quality of life. Even though some herbal therapies have promise, thorough scientific and clinical research is required to confirm their safety, dose, and long-term effectiveness. Therefore, rather than being used in place of traditional treatments, herbal medicine should be seen as a supporting therapy. To include these natural treatments in evidence-based sickle cell disease care, more studies and standardisation are necessary.

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