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Sickle Cell Anemia Its Epidemiology, Pathophysiology, Nutraceuticals Role: A Review

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ABSTRACT

The individual with the "SS" genotype possesses a deviant beta globin gene, resulting in the manifestation of sickle cell anemia, an inherited pathological condition. The severe symptoms of sickle cell disease are a result of a specific genetic mutation in the gene responsible for encoding the human β-globin subunit. This mutation leads to the substitution of valine for β 6 glutamic acid. The replacement of sickle cell hemoglobin (HbS) causes a significant decrease in its solubility when it is deoxygenated. The advancements in targeted molecular treatments have been driven by the significant advancements in our understanding of the biology of sickle cell disease (SCD) and its various repercussions since its discovery in 1910. Sickle cell disease (SCD) is a condition where the flow and lifespan of red blood cells are impacted by a mutated form of hemoglobin called hemoglobin S. This mutation occurs when a single amino acid in the β-globin chain is replaced, causing the hemoglobin to form polymers. During the early phases of treating sickle cell anemia, patients are commonly prescribed hydroxyurea, folic acid, amino acid supplements, penicillin prophylaxis, antimalarial prophylaxis, and blood transfusions to stabilize their hemoglobin level. They face significant expenses and hazards. However, there is a positive development: the investigation of medicinal plants for their ability to prevent sickling has yielded significant financial rewards. Laboratory experiments have demonstrated that this alternative therapy involving nutraceuticals can effectively reverse the process of sickling and also decrease the occurrence of crises.

Keywords- Sickle cell anemia, Pathophysiology, Nutraceuticals, Herbs.

I. INTRODUCTION

Herrick was the first to describe sickle cell disease (SCD) in 1910, despite evidence to the contrary. The disorder is the result of a mutation in the β-globin gene and can be inherited in either a homozygous or compound heterozygote form[1]. The replacement of the hydrophilic amino acid glutamic acid with the hydrophobic valine at the 6th position of the β-chain of haemoglobin, referred to as haemoglobin S (HbS), happens due to a single base-pair point mutation (GAG to GTG). Although Mendelian inheritance was well

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established, it was initially recognised at the molecular level by Pauling and then confirmed by Ingram to be caused by a single mutation in an amino acid roughly 70 years ago[2]. However, SCD stands out by displaying a variety of different clinical presentations, showing phenotypic heterogeneity. The level of foetal haemoglobin (HbF) starts to decrease towards the adult level when a child is between five and six months old. This decrease leads to acute and chronic challenges in sickle cell disease (SCD), which is a condition that affects multiple organs and systems in the body[3].

II. EPIDEMIOLOGY

Individuals of African, Indian, or Arab ancestry are particularly affected by sickle cell disease (SCD), which is one of the most prevalent genetic fatal conditions in humans. Sub-Saharan Africa (SSA) is responsible for the bulk of the world's over 300,000 births, with Nigeria and the Democratic Republic of the Congo being the most affected[4]. The prevalence of HbS carriers in West African countries ranges from approximately 25% to 33%, while in African Americans it is only around 0.01%, and it varies among European populations. Migration from countries with a high frequency of sickle cell disease (SCD) is causing a rise in the occurrence of the disease in developed nations. Like France, the United Kingdom has approximately 14,000 individuals residing with SCD[5].

However, nations such as Italy and Germany have experienced an increase in the number of patients coming from Africa. Individuals diagnosed with SCD are seeing higher rates of survival into adulthood and old age, causing a change in the age distribution of the condition from childhood to later stages of life. In comparison to the high death rate in Sub-Saharan Africa (SSA), where 50-90% of infants with sickle cell disease (SCD) do not survive beyond their first five years, recent reports show that over 94% of SCD-positive neonates in the United States, France, and the United Kingdom reach maturity[6]. Patients in countries lacking universal newborn screening or in situations with limited resources may perish prior to the identification of their diagnoses. Infections, severe anaemia (including acute splenic sequestration and aplastic anaemia), and multi-organ failure are the typical factors leading to death if early diagnosis is not accompanied by education, preventive medications (such as penicillin prophylaxis), and continuous monitoring. Thus, countries where sudden cardiac death is a significant issue in public health should give priority to the diagnosis of newborns and young infants[7].

Despite the multitude of public pronouncements by politicians and proclamations by international organisations, the majority of governments in Sub-Saharan Africa (SSA) still lack the financial means to carry out early diagnosis of newborns. Policymakers throughout the continent, particularly in India where the majority of sickle cell disease (SCD) cases occur, need to fully adopt screening measures in order to realise its significant advantages. In order to enhance health outcomes and overall quality of life, it is imperative to incorporate hydroxycarbamide therapy, penicillin V prophylaxis, and other preventive drugs such as antimalarials into comprehensive care[8].

III. PATHOPHYSIOLOGY

The vaso-occlusive pain crisis is the primary outcome associated with SCA. Vaso-occlusion, a complex phenomenon, is not the sole pathophysiological event in sickle cell anaemia[9]. The process of HbS polymerisation plays a crucial role. The polymerisation of haemoglobin S can cause injury to any organ due to the occurrence of haemolytic anaemia and blockage of blood flow, particularly in small veins but also in certain larger ones[10]. Patients with sickle cell anaemia have approximately 20% reticulocytes among their red blood cells, which are also capable of undergoing HbS polymerisation. Haemolysis can modify the course and impact of SCD through both direct and indirect mechanisms[11].

Furthermore, apart from the previously stated cellular abnormalities, HbS polymers also give rise to supplementary pathophysiological pathways that contribute to the overall development of sickle cell disease. The pathophysiology of SCD is consistent across different genotypes, such as SCA with modifying genes and double heterozygous conditions, as previously mentioned. Variants have the potential to reduce the severity of a condition or cause slight changes in observable characteristics.

During the process of deoxygenation within red blood cells, hydrophobic motifs on individual tetramers of deoxygenated (T-state) HbS become exposed in tissues that require a large amount of oxygen[12]. Thus, the formation of a HbS polymer initiates when βS-globin chains on different deoxygenated HbS tetramers join together, concealing the hydrophobic motifs. The rapid proliferation of these HbS polymers into extended fibres leads to a deformation of the erythrocyte membrane, resulting in cellular rigidity, energy depletion, desiccation, reduced fluidity, premature destruction of red blood cells, and the formation of sickle-shaped erythrocytes[13].

The concentration of foetal haemoglobin (HbF) has an inverse connection with the rate of polymerisation of HbS. This means that as the concentration of HbF increases, the rate of polymerisation decreases[14]. The rate of polymerisation is directly proportional to the concentration of HbS inside red blood cells, raised to the power of 34. Certain genetic variations or mutations, such as hereditary persistence of HbF or α-thalassemia, or the existence of the βC-allele in addition to the βS allele, can impact the degree of severity of the illness[15].

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IV. NUTRACEUTICALS

A nutraceutical is a precisely formulated product that has been scientifically developed to fulfill specific nutritional requirements and/or offer preventive healthcare[16]. Nutraceuticals, along with dietary supplements, aid in the prevention and treatment of diseases by providing formulated nutrients. The term "nutraceutical" was created by Dr. Stephen De Felice in 1989 by combining the phrases "nutrition" and "pharmaceutical." Consuming these foods or their constituents can aid in addressing a range of health conditions, including disease prevention and treatment[17]. The study of nutrition science has evolved into various areas, ranging from forecasting dietary shortfalls to gaining significance in human health and the prevention and treatment of chronic diseases. Since its first proposal by Dr. De Felice, the terms "nutraceuticals," "food supplements," and "dietary supplements" have emerged as descriptors for these products[18].

The current regulatory framework lacks a clear differentiation between nutraceuticals and food supplements. Recent studies have focused on reconsidering nutraceuticals in terms of their efficacy, safety, and toxicity. The intake of food, beverages, or other substances that provide nutrition is crucial for sustaining life, generating energy, and promoting growth. Extracting nutrients from various dietary items is a well-established and reliable process currently[19].

To differentiate between nutraceuticals and food/dietary supplements, the initial step is to determine an epidemiological aim. Subsequently, in order to comprehend the functioning process, investigations are carried out to assess the safety and effectiveness. In order to use a "nutraceutical" for treating a pathological disease, it is necessary to have substantial scientific evidence. One method of differentiating between the two types of formulations is to consider "food supplements" as substances that address deficiencies in micro- or macronutrients[20]. Nutritional supplements that have significant clinical proof are characterized by optimal bioavailability, low side effects, and a strong safety profile. The distinction between nutraceutical and food supplement formulations is indistinct; the same compounds can be used for either purpose, depending on the stated claims. Nutraceuticals encompass food products that are either pre- or pro-biotic, as well as food products with specialized medical uses, distinct from dietary supplements[21].

Conversely, nutraceuticals encompass dietary items that are abundant in minerals or vitamins, as well as functional foods and herbal medicines[22]. Integrating nutraceuticals into a standard diet can potentially reduce or eliminate the need for pharmaceuticals in those who are appropriate candidates for nonpharmacological treatments for a pathological ailment, hence aiding in the prevention of such disorders[23]. According to many assertions, spices and herbs have the potential to enhance health and prolong life by reducing the likelihood of various diseases. Nutraceuticals have demonstrated significant potential in combating and managing intricate illnesses, in addition to their various other applications. However, nutraceuticals necessitate prescription and administration, and they must be closely managed to prevent their unregulated usage and adverse consequences[24].

The effectiveness and absorption rate have been the primary areas of research in various studies exploring nutraceuticals derived from pharmaceutical ingredients. Even in pregnant women, many statins have been employed to prevent cardiovascular problems, while ensuring their safety and efficacy[25]. In order to avoid the occurrence of diabetes mellitus and hypertension, or to enhance the effectiveness of traditional medications, it may be suitable to consider using nutraceuticals that have a well-established safety record and a demonstrated positive impact on pregnancy. Some potential nutraceutical options to consider are folic acid, calcium, omega-3 polyunsaturated fatty acids, resveratrol, zinc, inositol, and probiotic supplements. Research has been carried out on the nutraceutical ezetimibe to help individuals who are at risk of developing cardiovascular diseases as a result of elevated levels of statins. Promising results have shown that the combination of a novel nutraceutical with non-steroidal anti-inflammatory drugs (NSAIDs) is beneficial and safe for treating osteoarthritis.

Nutraceuticals, such as antioxidants, omega-3 fatty acids, wheatgrass, aloe vera, seaweed, algae, ginseng, and Echinacea, maintain a robust and growing market. Based on a recent study, the global nutraceutical industry is expanding rapidly and has the potential to reach a value of $340 billion by 2024[26]. The projected compound annual growth rate (CAGR) for the nutraceuticals industry between 2016 and 2024 is 7.2%. The current boom in popularity of the nutraceuticals-based sector can be attributed to several factors, such as the growing demand for nutraceuticals, increased public awareness of the significance of nutrition, and a noticeable upward trend in the healthcare industry's growth rate[27].

The nutraceutical industry is projected to have a substantial growth from $247 billion in 2019 to $336 billion in 2023, exhibiting a compound annual growth rate (CAGR) of 8%. The majority of this market, accounting for 90%, is concentrated in Europe, the USA, and Japan. India and other emerging countries in Asia and the Pacific are currently the focal point for nutraceutical companies due to the maturation of global markets. In 2017, India accounted for only 2% of the global nutraceutical market[28]. The forecasts project a compound annual growth rate of 21%, resulting in a total of $11 billion by 2023. By 2023, India is expected to secure at least 3.5% of the global market share[29][30].

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V. NUTRACEUTICALS ROLE IN SICKLE CELL DISEASE

Nutritional problems are believed to worsen the severity of sickle cell disease. Due to the lack of any existing therapy or cure for sickle cell anemia, there has been a significant increase in efforts to advocate for the use of nutritional supplements as a potential form of treatment[31]. Sickle cell disease patients have higher caloric and protein requirements compared to healthy individuals. Patients who consistently consume a low number of calories are susceptible to undernutrition. There is a dearth of comprehension regarding the potential integration of nutrition with sickle cell medical services[32][33]. To enhance the management and treatment of SCD, particularly in Africa, it is imperative to increase awareness about the crucial role of nutrition. Nevertheless, it is essential to give priority to beneficial dietary suggestions, especially for children with SCD. Severe sickle cell disease (SCD) is exacerbated by continuous inflammation and oxidant stress, which intensify its effects. Incorporating nutritional management into supplemental care, in addition to usual practices, is essential. It is imperative to establish suitable reference intakes for patients with SCA[34].

Recent studies have demonstrated that malnutrition is a common occurrence in individuals with Sickle Cell Anemia (SCA). It has been suggested that frequent use of vitamin supplements can potentially alleviate this issue. At roughly 5 months of age, individuals may have symptoms such as pain, fatigue, frequent infections, organ damage, and premature mortality. However, it is important to note that these symptoms might vary from person to person[35].

As a result of these symptoms, children may experience a delay in their growth and development, leading to an increased requirement for calories and protein. Individuals suffering from sickle cell disease (SCD) may develop a condition known as leaky gut due to ongoing damage caused by ischemia-reoxygenation resulting from vaso-occlusive crises (VOC). This condition affects the concentration of microbiota, their ability to stick to the epithelial membrane, and the extent of translocation[36]. This has an impact on immunity, microbial imbalance, hormonal environment, metabolic homeostasis, and nutritional intake. Identifying gene-nutrient relationships to explain specific responses in various ethnic and environmental conditions is a challenging endeavor. The widespread presence of dietary deficits in SCD may contribute to more severe pain consequences. Given the intricate and wide-ranging nature of the nutrition problem, it is imperative to develop a fresh collaborative approach that can effectively tackle the diverse array of staple foods, their origins, micronutrients, and phytonutrients, all of which are crucial for human health and well-being[37]. The main priorities should encompass optimizing digestion, enhancing the human microbiota, promoting overall health, and fostering mental well-being. Children with hereditary diseases such as sickle cell disease (SCD) often experience dysphagia and feeding difficulties[38]. These issues arise from the intricate interplay of anatomical, physiological, pharmacological, and behavioral factors. If the child experiences feeding difficulties that result in food consumption becoming challenging, passive, or painful owing to symptoms such as shortness of breath, trouble speaking, choking, coughing, exhaustion, or vomiting, they may require their parent's assistance in feeding them[39]. Iron deficiency is not commonly seen in people with sickle cell disease (SCD), especially those with the most severe form of the disease caused by the homozygous SCA genotype. However, there has been limited research on the dietary consumption of iron in SCD patients, and there is a lack of clear guidelines for the restriction of dietary iron[40]. An important difficulty has arisen in precisely evaluating the amount of food consumed, the state of nutrition, the use of supplements (both with and without nutritional value), and the heightened vulnerability to infections caused by certain pathogens in these individuals, particularly in young children (those who are under 5 years old)[41].

Due to the absence of thorough data on dietary and nutritional intake in poor nations, the risk of a more negative prognosis in SCA has increased. When intending to boost the consumption of minimally processed foods, it is important to consider the beneficial benefits of antioxidants in combating SCA[42].

These individuals may have a higher vulnerability to inflammation, acute painful episodes, opportunistic infections, growth impairment, and deficits in essential nutrients. Deficiencies in iron, zinc, copper, folic acid, pyridoxine, and vitamin E, along with their associated problems, have been extensively researched and addressed for a considerable period[43]. The impact of folic acid supplementation on serum folate levels is not yet understood in relation to SCA. Randomized clinical research has investigated the efficacy of supplementing patients with sickle cell disease (SCD) with antioxidant nutrients in reducing hemolysis. The study found that even at low concentrations, vitamins C and E can enhance hemolysis[44]. Treatment with ὐ-3 fatty acids, zinc, and vitamin A was observed to enhance indirect hemolytic markers.

Early meta-analyses suggest that patients with SCD may experience advantages from using supplements that contain L-arginine, a semi-essential amino acid, or its precursors[45]. The production of L-arginine within the body is initiated by the transformation of proline, glutamate/glutamine, and the nonproteinogenic amino acid citrulline. L-arginine plays a crucial role in various essential activities such as cell division, wound healing, immune function, hormone secretion, and stimulation of protein synthesis[46].

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VI. ANTISICKLE HERBS

Alchornea cordifolia

Alchornea cordifolia is a shrub or small tree that is native to the tropical African region. The plant's leaves were examined for their aqueous and ethanolic extracts' capacity to prevent sickle cell development in vitro. The water-based extract exhibited a more potent anti-sickling effect[47]. The desiccated and pulverized botanical substance underwent multiple rounds of cold percolation using a blend of 95% ethanol and water, lasting for a period of 48 hours. The solvent was removed through evaporation following the screening of the fractions. The anthocyanins and alkaloids were removed thereafter using diethyl ether and distilled water. Prior to adding blood samples at different concentrations, the plant extract was diluted with a physiological solution. The impact of the A. cordifolia extract on cell sickling was evidenced by the restoration of normal erythrocytes in sickle blood samples treated with the extract. An increased concentration of extract leads to a more distinct normalization. The examination of the chemical screening results and the solubility of different chemical groups has led to the conclusion that the aqueous extract of *A. cordifolia* most likely exhibits its anti-sickling activity due to the presence of alkaloids or anthocyanins[48].

Hymenocardia acida

Hymenocardia acida is a little plant. This herb is commonly used, either on its own or in combination with other parts of the plant, for the treatment of SCD. The phytochemical screening of this plant's leaves revealed the presence of carbohydrates, tannins, flavonoids, saponins, alkaloids, resins, steroids, and terpenes[49]. It was shown that the effectiveness of ethanol extracts from the leaves in reversing sickled human RBCs was dependent on the dosage. Studies have shown that saponins have the ability to inhibit inflammation. After a duration of 30 minutes, the morphology of the red blood cells undergoes a transformation from a sickle shape to a typical biconcave shape, and they begin to increase in size.

Zanthoxylum heitzii

Currently, Africans utilize various plant extracts derived from the Rutaceae family to treat sickle cell condition (SCD). Only a limited amount of research has demonstrated that extracts derived from the genera Zanthoxyllum and Fagara has anti-sickling effects. This laboratory experiment studied the antioxidant and antisickling benefits of extracts from *Zanthoxyllum heitzii*. The compound sodium metabisulfite at a concentration of 2% was employed to induce the deformation of red blood cells (RBCs) known as sickling[50]. Afterwards, the sickled RBCs were subjected to treatment with extracts at different concentrations. The impact of *Z. heitzii* extracts on the stability of sickle cell membranes and the solubility of hemoglobin S can be examined by osmotic fragility tests. Qualitative phytochemical assays were conducted to evaluate the presence of alkaloids, tannins, saponins, flavonoids, glycosides, and phenols in each extract[51][52]. The antioxidant capacity of these extracts was assessed using quantitative techniques including Folin, Ferric Reducing Antioxidant Power (FRAP), and diphenyl 1, 2 picryl hydrazyl (DPPH). Sodium metabisulphite increased the percentage of red blood cell sickling from 29.62% to 55.46% within a two-hour period. The percentages of both induced and non-induced sickling cells were shown to decrease when sickling cells were subjected to treatment with extracts at different dosages. The *Z. heitzii* fruit extract had the highest efficacy in preventing sickling[53]. The optimal stability of the membrane cell was most effectively exhibited by the identical extract at a concentration of 250 µg/mL, in comparison to the other extracts. Although not as powerful as the gold standard, all of the extracts exhibited a certain level of antioxidant and anti-radical activity[54].

Uvaria chamae

The *Uvaria chamea* root extract, dissolved in water, was exposed to SS red blood cells at various concentrations. This exposure occurred either before or after the Emmel Test. The extract was incubated with hemoglobin, and the level of oxidative stress inside the red blood cells was assessed using the methaemoglobin assay[55]. An in vivo assessment was conducted to determine the impact of the extract on hemoglobin levels, mean corpuscular volume, and platelet counts in Wistar rats.When administered at concentrations of 40 and 20 mg/ml in the bloodstream, the extract successfully halted the generation of sickle cells ($P<0.05$). Furthermore, at a concentration of 40 mg/ml, it caused sickle cells to revert back to their normal biconcave shape ($P <0.05$). At a concentration of 10 mg/ml, it decreased the synthesis of methemoglobin, demonstrating its antioxidant activity. The extract did not induce erythropoiesis or thrombopoiesis in the treated rats, as evidenced by the absence of any significant increase in hemoglobin level, mean corpuscular volume, or platelet count. The extract of *Uvaria chamae* reduced the sickling of red blood cells in a manner that depended on the dosage. While it did reduce oxidative stress inside red blood cells, it did not exhibit any hematological action. Hence, it could be beneficial in managing or averting sickle cell crises, but it does not provide any assistance in addressing anemia[56].

VII. CONCLUSION

This study discovered that there is a high prevalence of herbs with antisickling properties in West Africa, and ongoing efforts are continuously uncovering new ones. Plants contain a large number of bioactive compounds, which have the potential to act as anti-sickling agents. These substances can help maintain a

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balance in oxidative processes by removing harmful free radicals. Nutraceuticals play a key role in the management of sickle cell disease. Herbs with scurvy-preventive properties are also beneficial in this treatment.

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