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Functional Foods and Nutraceuticals in the Primary Prevention of Sickle Cell Disease Crises

Review Article

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Abstract

Sickle Cell Disease (SCD) is a multisystem disease, associated with episodes of acute illness and progressive organ damage. Sickle cell disease is one of the most prevalent hereditary disorders with prominent morbidity and mortality. Currently, there is no widely available cure for sickle cell disease. Bone marrow transplants are potentially curative, but their use is limited due to the high cost of the procedure, the difficulty of locating appropriate donors, and the level of risk associated with the procedure. Therefore, we urgently need the therapeutic agents having easy availability, less cost and minimum side effects. However, a bright ray of hope involving research into antisickling properties of from foods, edible and medicinal plants has been rewarding. This alternative therapy using functional foods and nutraceuticals has proven to not only reduce crisis but also reverse sickling. The immense benefits of functional foods and nutraceuticals used in the management of sickle cell disease are discussed in this paper.

Keywords: Functional foods; Nutraceuticals; Primary prevention; Sickle cell disease crises

Introduction

Drepanocytosis also known as Sickle Cell Disease (SCD) or Sickle Cell Anemia (SCA) is a life-long blood disorder characterized by erythrocytes that assume an abnormal, rigid, sickle shape. It is a genetically inherited disease in which a single base substitution in the gene encoding the human β-globin subunit results in replacement of β6 glutamic acid by valine, leading to the devastating clinical manifestations of SCD [1].

This substitution causes drastic reduction in the solubility of sickle cell Hemoglobin (HbS) when deoxygenated. Under these conditions, the HbS molecules polymerize to form long crystalline intracellular mass of fibers which cause the deformation of the biconcave disc shaped erythrocyte into a sickle shape. The consequences of this defect are red cell membrane fragility, hemolytic anemia and tissue damage brought about by the blockage of blood vessels by the sickled cells. The complications can be severe and include retarded growth, periodic attacks of pain and progressive organ dysfunction leading in most cases to a much reduced life expectancy [2,3]. Oxidative stress has a major role in complicating anemia with other infectious diseases [4]. SCD patients experience increased oxidative stress compared to their healthy counterparts. Therefore, antioxidant capacity is vital in SCD to control the extent of tissue injury that may occur as a result of increased oxidative stress. SCD condition may further impair antioxidant demand as sickle erythrocytes may form clumps with healthy RBC damaging them and increase circulating reactive oxygen species such as superoxide's and hydroxyl radicals [5]. It is theorized that individuals who have characteristic hypermetabolic processes, such as SCD patients will require an increased antioxidant capacity to combat oxidative stress [6].

Despite its ubiquitous nature, sickle cell disease is an illness that affects especially black people [7]. The World Health Organization has estimated that each year 220,000 babies are born with SCD in Africa, and that SCD accounts for up to 16% of deaths of children aged < 5 years in some African countries [8,9]. The reported prevalence of the sickle cell trait in African-Americans varies from 6.7% to 10.1% and in Africans the range is from 10 to 40% across equatorial Africa and decreases to between 1 and 2% on the North African coast and less than 1% in South Africa [10,11]. The prevalence of the sickle cell trait

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varies widely worldwide and may be as high as 50% in certain regions [11,12]. The prevalence of SCA is approximately 1 in 600 newborn African-Americans infants and 150,000 to 300,000 newborn Africans [13,14].

Sickle cell crises have been investigated in top priority by researchers all around the world in order to explore effective therapy towards solving the sickle cell disease problem. The aim of this current paper was to examine the impact of functional foods and nutraceuticals in relation to the development and progression of SCD. Epidemiologic studies have long demonstrated the association between certain foods and edible plants patterns and SCD. Research into the antisickling potential of their bioactive compounds may support the development of functional foods and nutraceuticals.

Management of SCD

Even though people with sickle cell disease suffer from several pain crises every year, there is no cure for the majority of them. However, some researchers tend to manage people with sickle cell disease with therapeutics treatments, which means different options that available under health care professionals, such as preventive measures, symptomatic treatment, Bone-Marrow Transplantation (BMT) and some products having targeted pathways. All these kind of treatments aimed to reduce the number of pain crises in a year expect bone marrow transplant, which aimed to cure from sickle cell disease [15]. A bone marrow transplant is a procedure to replace damaged or destroyed bone marrow with healthy bone marrow stem cells from a donor. BMT is considered the only curative therapy available to date. The goal is to eliminate the sickle erythrocyte and its cellular progenitors and replace them with donor hematopoietic pluripotent stem cells that give rise to erythrocytes that express no sickle hemoglobin (HbS), thereby reducing HbS levels to those associated with the trait condition [16]. Bone marrow transplantation has recorded good curative results of some Central Africa SCD children living in Belgium [17-21]. Its application in Africa is difficult because of its highest cost (approximately one hundred and fifty thousand Euros) and lack of technical equipment [22]. The most popular approach to prevent or reverse sickling *in vitro* and *in vivo* is to employ compounds which directly affect the Hemoglobin (Hb) molecule. In developing countries, Foods, edible and medicinal plants have been used in the management of sickle cell crises associated morbidities among the less privileged classes of the society. Foods and plant extracts are found to possess properties which prevent the erythrocytes from deforming and losing its integrity. In the treatment of SCD, it is required that one focuses on the ways of inhibiting sickle cell hemoglobin polymerization, prevention or repair of red cell dehydration and interrupting the interaction of sickle cells with the endothelium.

Bioactive compounds from foods, edible and medicinal plants used in SCD management: Bioactive compounds from foods, edible and medicinal plants, known as antisickling agents, which improve the health of sickle cell individuals are rich in proteins, amino acids, unsaturated fats, phenolic compounds, vitamins and minerals which are thought to be responsible for their observed antisickling action [23]. Following reports on the antisickling potentials of foods plant extracts, efforts to identify the causative agent behind it was initiated. There is an array of reports on the various bioactive compounds constituents of different plant extracts. Among the role of various bioactive compounds in the management of SCD, antisickling effects of different substances have been investigated. Food and edible plant demonstrates its importance in alimentation and daily intake. Many plants constituent have been investigated for their anti-oxidative properties. Antioxidant intake protects individuals from oxidative damage of in vivo lipids and proteins [24]. Antioxidants (scavengers of free radicals) are believed to be major components of these antisickling agents that add to their potential. The higher its possible antisickling effect as this enables it to reduce oxidative stress that contributes to sickle cell crisis [25]. Increased antioxidant intake may be beneficial for SCD clients as they support cell turnover and RBC formation [26,27]. Phenolic compounds are important components in vegetable foods, infusions, and teas for their beneficial effects on human health. *Carica papaya* is native to Nigeria and Central America, and is medicinal plant used as an alternative therapeutic agent for SCD. Phenolic compounds extract like 5,7-Dimethoxycoumarin and polar molecules such as protocatechuic acid, p-coumaric acid, chlorogenic acid, kaempferol and quercetin were detected and identified in qualitative analysis. Quantitative analysis showed the presence of phenolic acids as the main compound, while chlorogenic acid was found in trace amounts, compared to the flavonoids and coumarin compounds have been found in papaya leaves. The extract has antisickling effect and revealed appreciable membrane stabilizing (protective) [28]. Among the important ones are the three isomeric of divanilloylquinic acids (3,4-O-divanilloylquinic acid; 3,5-O-divanilloylquinic acid and 4,5-O-divanilloylquinic) and 2-dihyroxymethyl benzoic acid isolated and identified from *Fagara zanthoxyloides* in the treatment and management of SCD was demonstrated [29-31]; stabilizes the red cell membrane [32]; also activates the red cells membrane-bound enzymes Na^+, K^+-ATPase and Ca^{++}-ATPase, which are involved in the sickling process [33]. 2-hydroxymethylbenzoic acid as an anti-sickling agent from the root of *Zanthoxylum macrophylla* roots; produced stabilization of the erythrocytes membranes [31,34].

There are several compounds such as amino acids, which prevent sickling by affecting the erythrocyte membrane, causing an increase in the cell volume of the erythrocyte and thus reducing the intracellular hemoglobin concentration below its minimum gelling concentration [35,36]. Of all the amino acids reported, phenylalanine was shown to be most active [36,37]. L-Arginine decreased oxidative stress and L-Glutamate decreased resting energy expenditure [38,39]. Several researchers have reported cases of synergy among short and long polypeptide fragments used as anti gelling agents [40].

Omega-3 fatty acids decrease in number of pain episodes and thrombotic activities. More recent reports of feeding high protein and L-Arginine supplements and n-3 fatty acids to HbS have shown significant reductions in inflammation, oxidative stress, red cell density and pain episodes, and improved microvascular function [41]. Many dietary supplements, such as thiocyanate agent possessing immense potential to inhibit erythrocytic deformations have been reported to be beneficial in the management of sickle cell disease [42].

Researchers proved experimentally and clinically that antioxidant is crucial in healing and preventing sickle cell disease. Minerals and vitamins are important to be supplied constantly for maintaining hydration and membrane integrity. Vitamin E, beta-carotene, and

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vitamin C are all powerful natural antioxidants. Many clinical trials have shown that antioxidants such as vitamin E improve hemolysis, by longer erythrocyte lifespan; in elevated hemoglobin level [43,44]. Treatment with high doses of vitamin E reduces oxidative stress-induced erythrocyte injury [45,46]. Vitamin E decreased lipid peroxidation and improved erythrocyte membrane stability [47]. Vitamin C prevents in vitro Heinz Body (denatured Hb) formation in sickle red cells and normalizes blunted hemodynamic changes associated with posture adjustments [48]. Folic acid (B9) use makes this the most popular vitamin in the management of HbS. This treatment is based mainly on preventing deficiency from increased folate turnover, as in any chronic hemolytic anemia combined with limited reports of megaloblastic changes in HbS, responsive to folate supplementation [49]. Folic acid supplementation to reduce their high risk for endothelial damage [50].

About minerals, Oral magnesium supplementation reduces the number of dense erythrocytes and improves the erythrocyte membrane transport abnormalities of patients with sickle cell disease [51]. Magnesium decreases frequently the painful days and the length of hospital stay [52]. Zinc improved thymulin activity and decrease in frequency of bacterial infection (and hospitalization from painful crises, improved sexual maturation and reproductive capacity. Improvement in linear growth [53].

Vitamins and mineral are naturally present in some foods, added to others, and available as a dietary supplement. Zinc can found in various foods, including lean red meats, seafood (especially herring and oysters), peas and beans. Zinc is also found in whole grains. The resources of food that rich in magnesium and calcium are beans, nuts and wheat bran, raisin bran cereal. Vitamin E and beta-carotene are available in the following foods: vegetable oils (such as wheat germ, sunflower, safflower, com and soybean oils), nuts (such as almonds, peanuts and hazelnuts/filberts), seeds (such as sunflower seeds), green leafy vegetables (such as spinach and broccoli) and fortified breakfast cereals, fruit juices, margarine, and spreads. Ascorbic acid is widely distributed in nature, mostly rich in fresh fruits and leafy vegetables such as guava, mango, papaya, cabbage, mustard leaves and spinach. Animal sources of this vitamin such as meat, fish, poultry, eggs and dairy products contain smaller amounts and are not significant sources. Dark green vegetables like broccoli and spinach and dried legumes such as chickpeas, beans and lentils are naturally good sources of folate [54].

Functional foods and nutraceuticals are becoming more popular and readily available in many nations, with a potential large market in a few years to come. Their consumption has been associated with healthy aging, prevention and treatment of chronic diseases. Functional foods and nutraceuticals come from easily accessible natural resources. They are therefore a path to be exploited and implemented for the management of crises in sickle cell disease in developing countries.

Functional foods

In 1994, the US Institute of Medicine's Food and Nutrition Board defined functional foods as "any food or food ingredient that may provide a health benefits beyond the traditional nutrients it contains" [55].

Functional foods are similar in appearance to conventional foods; the former being consumed as part of the normal diet. In contrast to conventional foods, functional foods, however, have demonstrated physiological benefits and can reduce the risk of chronic disease beyond basic nutritional functions. When food is being cooked or prepared using "scientific intelligence" with or without knowledge of how or why it is being used, the food is called "functional food". Thus, functional food provides the body with the required amount of vitamins, fats, proteins, carbohydrates, etc., needed for its healthy survival [56].

Nutraceuticals

The term Nutraceuticals was introduced in 1989 by the US Foundation for Innovation in Medicine and referred to "any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease" [57]. Nutraceuticals provide an opportunity to improve the human health, reduce health care costs and support economic development in rural communities. The phrase "Let food be the medicine and medicine be the food", coined by Hippocrates over 2500 years ago is receiving a lot of interest today as food scientists and consumers realize the many health benefits of certain foods [58].

It should be noted that the term nutraceuticals, as commonly used in marketing, has no regulatory definition[59]. Nutraceuticals is a new term used to describe health-promoting foods or their extracted components. Although debate continues regarding the exact meaning of these terms, it is convenient to consider nutraceuticals as healthful products that are formulated and taken in dosage form (capsules, tinctures, or tablets). The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ. According to DeFelice, nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease. A nutraceuticals is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with foods and demonstrated to have a physiological benefit or provide protection against chronic disease [60,61]. Nutraceuticals are used as conventional foods or as sole items of a meal or diet [62].

Functional foods and nutraceuticals in sickle cell disease management

Bioactive nutrients and non-nutrient compounds have raised interest in human nutrition and health. Several naturally derived food, edible and medicinal plants substances have been studied in SCD therapies. Nicosan (formerly known as Niprisan), an anti-sickling phytomedicine (bioactive non-nutrient plant compounds), is reported to inhibit the polymerization of the hemoglobin S. As reported earlier, it is a cocktail of four medicinal plants, *Piper guineense*, *Pterocarpus osun*, *Eugenia Caryophyllus* and *Sorghum bicolor* as components and is currently being marketed in Nigeria in encapsulated [63]. Ciklavit is a plant extract preparation available for the management of the sickle cell anemia condition. It contains

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primarily extracts of the plant *Cajanus cajan* proteins (essential amino acids), vitamins such as vitamin C (ascorbic acid), and minerals such as zinc. Ciklavit (*Cajanus cajan* extract) has been reported to have antisickling properties and to improve well being of sicklers [35]. The role played by other components in Ciklavit (besides *Cajanus cajan*) is basically nutritional. Ciklavit may cause a reduction in bone pains (painful crises) and may ameliorate the adverse effect of sickle cell anemia on the liver [64].

Studies indicate that vitamin-mineral supplements of certain nutrients (vitamins C and E, zinc, and magnesium) or treatment with a combination of high-dose antioxidants can reduce the percentage of irreversibly sickled cells [65,66]. Zinc sulphate appears to help reduce red blood cell dehydration. Important studies indicate that it helps prevent sickle cell crises and reduce pain and life-threatening complications. A study on children with sickle cell suggested that supplements may help improve growth and weight gain. It may also boost the immune system and help protect against bacterial infections. Zinc deficiency is a common nutritional problem in sickle cell disease, so supplements may be important. Magnesium protects against potassium and water loss in sickle cells [53,67].

Many sources of constituents capable of ameliorating the sickle cell crises have been investigated with a view to contributing to the search for substances (proteins, amino acids, unsaturated fats, phenolic compounds, vitamins and minerals) that would be effective in solving the sickle cell disease problem. Black beans seeds (*Phaseolus vulgaris* L.); mill wild variety (*Fragaria vesca* L.); bitter kola (*Garcinia kola* H.); *Annona muricata* L.; *Azadirachta indica* J. in form part. This is the ethno-botanic investigation that we carried out in this area to know how populations of this locality manage SCD [68]. Certainly, these products will constitute a new base of natural products for the formulation of functional foods/nutraceuticals being able to manage sickle cell disease.

While many of these 'natural' compounds have been found to have high therapeutic potential; future studies should include well-designed clinical trials assessing combinations of these compounds to realize possible synergies they bring into human health.

Conclusion

For sickle cell disease challenges in drug research and development, researchers must be focused on decreasing the number of crises. Various bioactive components in the foods, edible and medicinal plants extracts may be isolated and developed to drugs future. Some research on identifying the bioactive components to experimentally examine their individual potential for controlling the sickle cell disease is in progress. Research into foods, edible and medicinal plants is a current trend in the management of tropical diseases and genetic disorders like sickle cell disease, with a view to finding cheaper, alternative medicines that the wide populace can have immediate access to. The work outlined in this paper, indicate the feasibility of botanicals, mainly antisickling functional foods and nutraceuticals, as attractive potential candidates for sickle cell disease management and strongly collaborate the foods, edible and medicinal plants as main basis of formulation of functional foods and nutraceuticals.

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