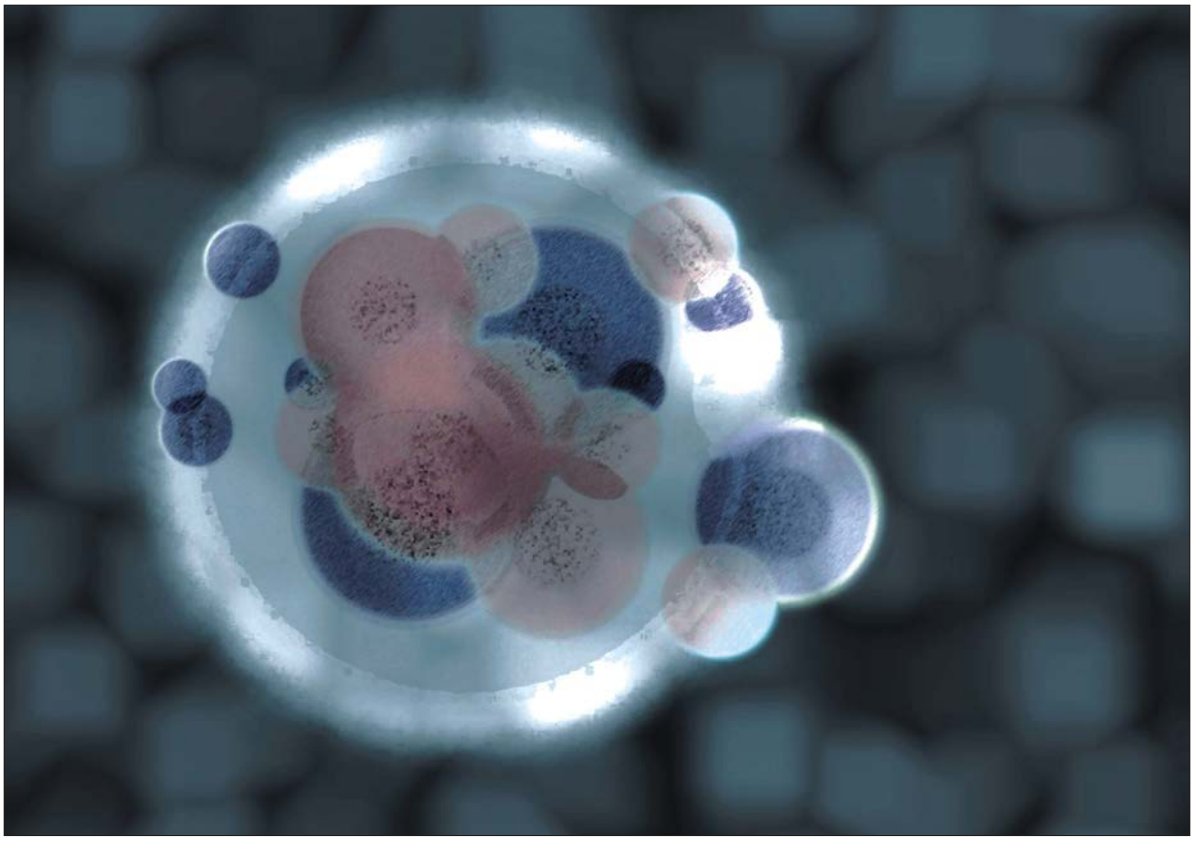

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Management of Sickle Cell Anemia in Nigeria with Medicinal Plants: Cationic Evaluation of Extracts and Possible Effects on the Efficacy

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Abstract: Eleven aqueous plant extracts from 8 traditionally used Nigerian medicinal plants *Adasonia digitata* L. (Bombacaceae), *Bryophyllum pinnatum* Lam. (Crassulaceae), *Cajanus cajan* (L.) Mill sp. (Fabaceae), *Carica papaya* L. (Caricaceae), *Cissus populnea* Guill and Perr (Vitaceae) *Parquetina nigrescens* (Afzel.) Bullock (Periplocaceae), (*Terminalia catappa* L.) (Combretaceae) and *Zanthoxylum xanthoxyloides* (Lam.) Waterman (Rutaceae) were evaluated for their cationic constituents as a measure of their efficacy in sickle cell anemia disorder. Extracts were subjected to dry ash digestion and the resultant supernatants were used for macro- and micronutrients determination using the emission flame photometer and the absorption spectrophotometer. K^+, Na^+, Fe^{2+} and Zn^{2+} were relatively higher than Ca^{2+} and Mg^{2+} in the tested extracts. The presence of these cations, K^+, Na^+, Ca^{2+} and Mg^{2+} implicated in the process of sickling and involved in electrolytes movement in the physiological system of the body may be an important parameter in sickle cell anemia management.

Key words: Sickle cell management, Nigerian medicinal plants, cationic evaluation

INTRODUCTION

Genetically, sickle cell anemia disease is believed to have originated from the sub-saharan black African population. Frequent abnormal hemoglobin like Hb S, Hb C, Hb E, thalassemia and glucose-6- phosphate dehydronenase deficiency are now evident.

Cell dehydration is an important characteristic of the sickle erythrocyte, it accelerates polymerization of the deoxy Hb S[1]. The formation of polymers and their explosive growth in the erythrocyte is preceded by a latency phase. This latent or delay time phase is inversely proportional to the15th-35th power of Hb S concentration. It is believed that this delay time plays a crucial role in the pathophysiology of sickle cell anemia disease[2]. Accordingly, a small change in the Hb S concentration has a marked effect on the Hb polymerization and sickling. Intracellular concentration of Hb S becomes high due to loss of K^+, Cl^- and water. The resulting dense cells play important roles in the pathophysiology of the vaso-occlusive events of sickle cell anemia disease. The loss of K^+ is partially offset by the increase in cell Na^+that could be due to cell membrane damage or an increase in Na^+ leak and the relative Na/K pump inhibition[3].

K^+ loss also results from the dislodgement of iron from its compartments, leading to deposition of denatured hemoglobin, ferritin, free heme and iron onto the cell membrane.

Four cations come into prominence in the modulation of ion pathways involved in the dehydration process and ensuing electrolytes imbalances triggered by diffusional and osmolytical activities. These cations are K^+, Na^+, Ca^{2+} and Mg^{2+}. Increase in intracellular free Ca^{2+} occurs during sickling, resulting in a large loss of K^+ with accompanying movements of Cl and water. The need to modulate the free Ca^{2+} arises during sickling to bring about reduction in that cationic concentration[4].

The activity of K^+/Cl co-transport is to a great extent modulated by the red blood cells Mg^{2+} content. Deoxygenation increases membrane permeability to Mg^{2+} in dense sickle cells and a net loss of intracellular Mg^{2+} occurs. Increased free cell magnesium levels reduce volume sensitive flux via K^+/Cl^- co-transport in both SS and AA cells. Modulating cellular Mg^{2+} concentration has been shown to affect this ion pathway[5]. Increase in cellular Mg^{2+} above physiological levels decreases the activity of the K^+/Cl^- co-transport markedly. It is therefore possible to inhibit cell dehydration via the K^+/Cl^- co-

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transport system by cellular modulation of Mg^{2+}. Diffusional fluxes of Na^+, K^+, Ca^{2+} and Mg^{2+} have been shown to occur in deoxy SS red blood cells along the sickling induced leak pathways[3]. There is an inward movement of Na^+ and outward flux of K^+, which are balanced with no net change in cell volume or ion content. An increase in cellular Na^+ activates the Na^+/K^+ ATPase pump, which may also contribute to cellular dehydration.

In the quest for a potential therapeutic strategy for the management of this seemingly incurable disorder, two options have become available. Either decrease the intracellular Hb S concentration through the use of agents capable of synthesizing fetal hemoglobin, Hb F, or inhibit sickle cell dehydration and K^+ loss through the use of erythrocyte active cationic agents capable of modulating the various cations implicated in the pathophysiology of sickling[6]. Such agents must be capable of inhibiting dehydration and K^+ loss by blocking the red cell membrane ion pathways, activated in the process of sickling.

The cationic involvement in the pathogenesis of sickling and the therapeutic strategies for future treatment options in sickle cell anemia disease necessitated the evaluation of the eight common traditionally used medicinal plants in Nigeria for their cationic contents and the possible effects of these cations on the efficacy of extracts of these plants as antisickling agents.

MATERIALS AND METHODS

Collection of plant materials: Plant materials were collected from different locations in the South Western part of Nigeria between October to December 2003. They were authenticated at the Forestry Research Institute of Nigeria Herbarium, Ibadan, Nigeria.

Extraction of plant materials: The plant materials were dried when necessary in the oven at 37°C and 200 g of each material was weighed and soaked in 1 L of distilled water in 2 L conical flask for 7 days stirring daily. At the end of the maceration, each macerate was individually filtered and then concentrated over the steam bath. Percentage yields were calculated with reference to the air-dried plant material. The resultant extracts were stored in the refrigerator until when needed for cationic analysis.

Cationic analysis: The extracts were subjected to dry ash digestion, and the resultant supernatants were used for macro-and micro-nutrient determination using the Corning 400 emission flame photometer and the Buck scientific atomic absorption spectrophotometer. Cationic contents of the extracts were determined based on standard procedures and the results.

RESULTS AND DISCUSSION

An insight into the therapeutic strategies and treatment options for sickle cell anemia disease may be gained from the understanding of electrolytes imbalance in sickle cell anemia disease. The dehydration that takes place during sickling and the loss of K^+ due to the increase in cell membrane permeability to Ca^{2+} activates the Gardos channel and induces diffusional flux of Na^+. The Na^+/K^+ ATPase pump activated by the increased Na^+ leads to further cell dehydration and K^+ efflux[7]. Additional K^+ loss occurs as a result of low cellular Mg^{2+}, which activates the abnormal activities of the K-Cl co-transport system leading to further cell dehydration in deoxy Hb S. K^+, Na^+, Mg^{2+} and Ca^{2+} and water are the major electrolytes involved in the electrolytes imbalance theory, which by osmolytic and diffusional processes could correct the imbalance and reverse the physiological processes observed during sickling. From Table 1, the dried red seeds of *C. cajan* had the highest yield while the fresh green leaves of *B. pinnatum* had the lowest yield to solvent.

A therapeutic dosage regimen of low and high comes into play, high K^+, low Ca^{2+} and high Mg^{2+}. It is also desired to have low Na^+, but the low and high modulation of K^+, Ca^{2+} and Mg^{2+} are relevant in the SS erythrocytes. Based on the low-and-high modulation, it is possible to assess and rationalize why some of these antisickling agents have not been as efficacious as the traditional medical practitioners had proclaimed. From (Table 2), none of the medicinal plant extracts totally satisfied the low and high requirement of an imbalanced electrolyte system. *A. digitata* has a good high $K^+$and high Mg^{2+}, but a high Ca^{2+} would not be effective in an increased free intracellular Ca^{2+} environment as with the activated gardos channel. *P. nigrescens* could be an improvement on *A. digitata* based on the Ca^{2+}. The green leaves of *T. catappa* have high K^+ and good low Ca^{2+}, but the Mg^{2+} is low as with *C. populnea*. A system with a relatively high Mg^{2+} would be needed to decrease the abnormal activities

Table 1: Percentage water soluble plant extracts analyzed for cationic contents

Plant name	Morphological part used.	Yield (%)
Adasonia digital	Dried bark	19.30
Bryophyllum pinnatum	Fresh green leaves	13.00
Cajanus cajan	Dries red seeds	62.00
Carica papaya	Fresh unripe fruit	61.20
Cissus populnea	Fresh roots	44.87
Cissus populnea	Dried roots	25.50
Parqnetina nigresceus	Dried roots	14.00
Terminalia catappa	Ripe fresh fallan leaves	17.30
Terminalia catappa	Plucked green leaves	19.84
Terminalia catappa	Ripe fallen dried leaves	28.14
Zanthoxyium xanthoxyloides	Dried roots	15.60

Table 2: Cationic analysis of plant extracts used in Nigeria for the management of sickle cell anemia disease

Samples	Ca^{2+} (%)	Mg^{2+} (%)	K^{+} (%)	Na^{+} (ppm)	Fe^{2+} ppm	Zn^{2+} (ppm)
Adasonia digitata (dried bark)	1.01	1.07	5.26	112.61	33.00	20.06
Bryophyllum pinnatum (fresh leaves)	2.04	0.19	0.93	94.53	39.80	52.29
Cajanus cajan (dried seeds)	0.04	0.09	1.65	384.62	23.18	25.25
Carica papaya (fresh unripe fruit)	0.05	0.04	0.54	105.66	52.43	4.97
Cissus populnea (fresh roots)	0.03	0.05	0.12	67.52	49.11	15.37
Cissus populnea (dried roots)	0.04	0.21	2.51	325.60	52.76	41.73
Parqnetina nigresceus (dried roots)	0.65	1.04	3.06	227.11	76.69	99.30
Terminalia catappa (fresh fallen leaves)	0.76	0.32	1.40	636.56	83.18	23.43
Terminalia catappa (dried fallen leaves)	0.85	0.87	1.46	643.47	44.73	46.31
Terminalia catappa (dried green leaves)	0.19	0.31	3.91	549.69	20.79	32.24
Zanthoxylum xanthoxyloides (dried roots)	0.86	0.22	1.68	361.52	86.90	20.50

of the KCC system. It would seem that a combination of two of these herbs would be a more effective antisickling agent than what the traditional medical practitioners are now offering. A combination of *A. digitata* bark and *C. populnea* roots or *T. catappa* green leaves would be more satisfactory. This suggestion would be in line with the results obtained by Apovo *et al.*[8] that both the Gardos pathway and the K^{+}/Cl^{-} co-transport system are activated in whole SS RBC blood.

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