

UNIVERSITY OF PORT HARCOURT

**MANAGING THE SCOURGE OF SICKLE
CELL HAEMOGLOBINOPATHY:
WHICH WAY FORWARD?**

An Inaugural Lecture

By

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ORDER OF PROCEEDINGS

2:45pm: Guests are seated
3.00pm: Academic Procession Begins

The Procession shall enter the Ebitimi Banigo Auditorium, University Park and Congregation shall stand as the procession enters the hall in the following order:

ACADEMIC OFFICER
PROFESSORS
DEANS OF FACULTIES
PROVOST COLLEGE OF HEALTH SCIENCES
REGISTRAR
ORATOR
LECTURER
DEPUTY VICE-CHANCELLOR (ACADEMIC)
DEPUTY VICE- CHANCELLOR (ADMINISTRATION)
VICE-CHANCELLOR

After the Vice-Chancellor has ascended the dais, the congregation shall remain standing for the University of Port Harcourt Anthem. The congregation shall thereafter resume their seats.

THE VICE-CHANCELLOR'S OPENING REMARKS

The Registrar shall rise, cap; and invite the Vice-Chancellor to make his Opening Remarks.

THE VICE-CHANCELLOR SHALL THEN RISE, CAP AND MAKE HIS OPENING REMARKS AND RESUME HIS SEAT.

THE INAUGURAL LECTURE

The Registrar shall rise, cap and invite the Orator, **Prof. G. C. Obute**, to introduce the Lecturer.

The Lecturer shall remain standing during the introduction. The Lecturer shall step on the rostrum, cap and deliver his Inaugural Lecture. After the Lecture, he shall step towards the Vice-Chancellor, cap and deliver a copy of the Inaugural Lecture to the Vice-Chancellor and resume his seat. The Vice-Chancellor shall present the document to the Registrar.

CLOSING

The Registrar shall cap and invite the Vice-Chancellor to make his Closing Remarks.

The Vice-Chancellor shall then rise, cap and make his Closing Remarks. The Congregation shall rise for the University of Port Harcourt Anthem and remain standing as the Academic (Honour) Procession retreat in the following order:

THE VICE- CHANCELLOR

DEPUTY VICE-CHANCELLOR (ADMINISTRATION)

DEPUTY VICE-CHANCELLOR (ACADEMIC)

LECTURER

ORATOR

REGISTRAR

PROVOST COLLEGE OF HEALTH SCIENCES

DEANS OF FACULTIES

PROFESSORS

ACADEMIC OFFICER

PROTOCOL

Vice-Chancellor sir,
Deputy Vice-Chancellors,
Members of the Governing Council,
Registrar and other Principal Officers of the University
Provost College of Health Sciences,
Deans of Faculties,
Heads of Departments and Directors of Institutes,
Distinguished Professors and Colleagues,
Students of the University of Port Harcourt,
Distinguished guests,
Ladies and Gentlemen.

With great pleasure, I welcome you all to this inaugural lecture.

ACKNOWLEDGEMENTS

Vice-Chancellor Sir, I would wish to start by acknowledging the Almighty God who made this day possible. May He be praised and glorified. Having done this, I would then express my gratitude to my late father, Pa Francis Uwakwe, who laid a solid foundation for us his children quite early in our lives. Indeed, his fatherly care and vision propelled us to the great heights of life. Next would be my beloved mother, Mrs Margaret Uwakwe who has remained an ocean of inspiration for her children and all who come in contact with her. Mummy, you are the best! I would not fail to mention my siblings, Patty, Kenneth, Elizabeth and Anthony. Their love and encouragement are indelible in my memory.

I acknowledge the contributions of some of my teachers/lecturers at various points of my academic training, but notably Professor Emeritus E. O. Anosike, Late Prof, G.I.Ekeke, Prof, E.O.Ayalogu, Prof.(Mrs.) B.W.Abbey, Prof. M.O.Monanu, Prof.P.O.Uadia and Prof.(Mrs.) J.O.Akaninwor. I must not forget Prof. C. Ojinnaka, who inspired me to take up the lecturing job, and Prof. B.J.O.Effiuwewwere who encouraged me to pursue excellence. My colleagues and students of the Department of Biochemistry, University of Port Harcourt deserve mention too as they were part of my success story. I deeply appreciate my amiable wife, Mrs Theresa Uwakwe, and our children (Michael, Favour, Maximus, Daniel and Bliss) for the understanding and conducive home atmosphere that allowed me to reach the level of academic achievements that provided the knowledge I will impart in this lecture. To my students (undergraduate and postgraduate) and colleagues in the Department, and all those I could not mention due to exigencies, thanks for being there for me. Thanks a million!

Moreover, I wish to thank the Vice Chancellor for giving me the opportunity to deliver the 132nd Inaugural lecture of this unique University today.

Finally, I dedicate this lecture to the memory of Late Prof. G. I. Ekeke, who pioneered sickle cell research in the department of Biochemistry of this University. May his soul rest in peace. **“Let all that hath breath praise the Lord. Praise ye the Lord.” Psalm 150 v. 6 (KJV)**

MANAGING THE SCOURGE OF SICKLE CELL HAEMOGLOBINOPATHY: WHICH WAY FORWARD?

KEY POINTS TO BE ADDRESSED

- * What is Sickle Cell Haemoglobinopathy (SCH)?
- * How is SCH inherited?
- * What are the symptoms and complications of Sickle Cell Haemoglobinopathy?
- * Possible triggers of the Sickling phenomenon
- * What are the available classical approaches for the management of SCH? *Is there any cure for SCH?
- * The natural alternatives to SCH management.
- * Which way forward?

INTRODUCTION

WHAT IS SICKLE CELL HAEMOGLOBINOPATHY?

Sickle-cell Haemoglobinopathy or Sickle cell disease

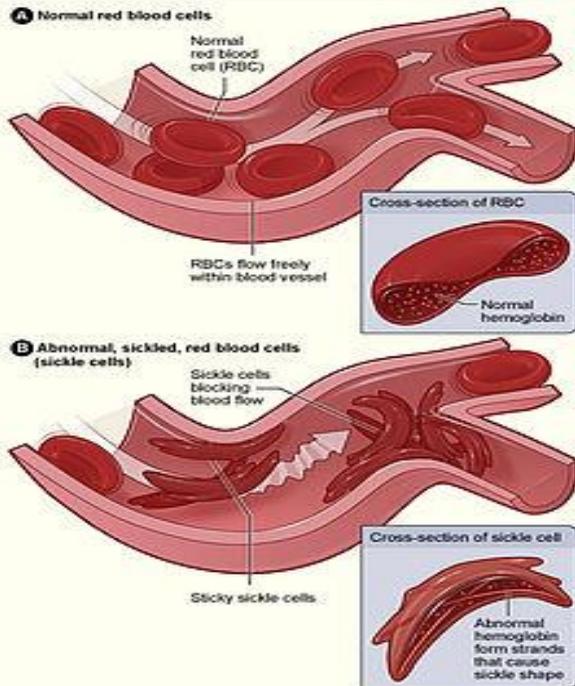
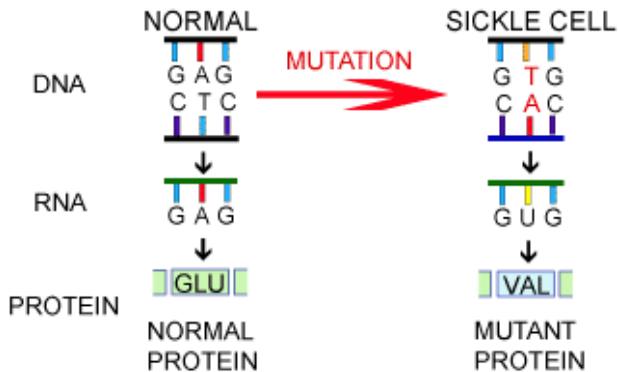


Figure 1 shows normal red blood cells flowing freely through veins. The inset shows a cross section of a normal red blood cell with normal haemoglobin. Figure B shows abnormal, sickled red blood cells log jamming, sticking and accumulating at the branching point in a vein. The inset image shows a cross-section of a sickle cell with long polymerized HbS strands stretching and distorting the cell shape. (Wikipedia, the free encyclopedia, August, 2015)

Sickle cell haemoglobinopathy is also known as sickle-cell disease (SCD), or sickle-cell anaemia (SCA) or sometimes drepanocytosis. This abnormal blood condition is also identified as ABIKU, OGBANJE and SANKARA MIJI, by the Yoruba, Ibo and Hausa-Fulani tribes of Nigeria (Ameh *et al.*, 2011, 2012). It is a hereditary blood disorder, characterized by an abnormality in the haemoglobin molecule of erythrocytes. The disease results from a substitution of the amino acid glutamic acid with valine (another amino acid) at position six of the beta globulin chain of haemoglobin. At the level of the genome, it is as a result of point mutation at position six of the beta globin gene in which the **codon** for glutamic acid (GAG) is substituted with that for valine (GTG). This leads to a propensity for the cells to assume an abnormal, rigid, sickle-like shape under conditions of hypoxia.



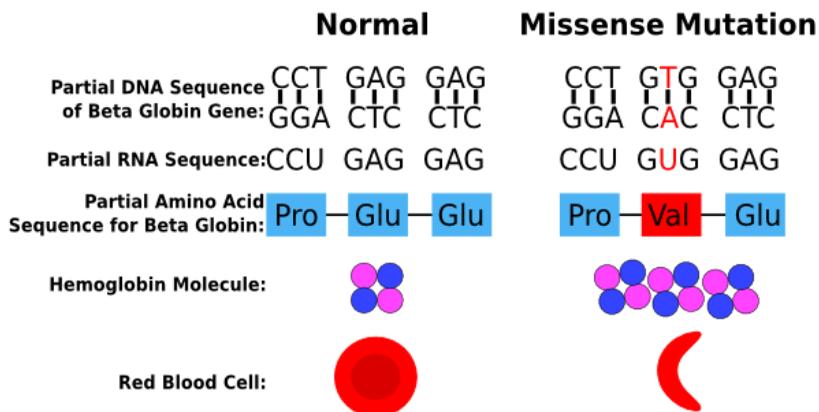


Figure 1B. Illustrations of Sickle Cell mutation

Sickle-cell disease is associated with a number of acute and chronic health problems, such as severe infections, attacks of severe pain ("sickle-cell crisis"), and stroke, and there is an increased risk of death (Yawn *et al.*, 2014).

Even though SCH has extensively been studied within the '*Homo sapiens*' (man), we have discovered the existence of haemoglobin polymorphs in other vertebrate species such as fish, lizard, mice, rat, chicken, goat, sheep and cow (Ekeke and Uwakwe, 2004; Chuku and Uwakwe, 2010a, b; Chuku and Uwakwe, 2012a, b.). These polymorphs exhibited electrophoretic patterns similar to those of man i.e. AA, AS, SS, SC, SD etc.; suggesting that the occurrence of mutant haemoglobins is not limited to the *Homo sapiens*. As a further confirmation of the possible nature of these haemoglobin types, the HbSS, HbCC, and HbSC-type erythrocytes of mudskipper (Goby I), African Sleeper (Goby II), mullet and Tilapia were subjected to sickling using 2% sodium metabisulphite to induce hypoxia. The results proved quite a spectacle in that results were similar to those of human blood. The HbSS-type erythrocytes of Goby-I and Goby-II sickled phenomenally as human HbSS erythrocytes. Indeed sickling was difficult to achieve using the HbCC and HbSC-type erythrocytes of mullet and tilapia similar to observations in human blood with similar haemoglobin types

(Chuku and Uwakwe, 2012a). It would however, be very naive at this stage to assume conclusively about the exact similarity of these non-human haemoglobin variants to those of human as definite conclusions are only possible when other biochemical techniques such as globin sequencing is performed. But migration patterns of the haemoglobins of these vertebrates are very revealing and obviously point to similarities in the charge properties of the haemoglobin polypeptides of man; this offers the possibility of using these vertebrates as models in sickle cell research.

Table 1. *Blood groups, rhesus factors and Hb genotypes of goat (Capra hircus-L) (Chuku and Uwakwe, 2010).*

S.No	Blood group	Rhesus factors	Genotype
Gi	‘O’	RhD ⁻	AA
Gii	‘O’	RhD ⁻	AS
Giii	‘O’	RhD ⁻	AS
Giv	‘O’	RhD ⁻	AA
Gv	‘O’	RhD ⁻	AA
Gvi	‘O’	RhD ⁻	AS
Gvii	‘O’	RhD ⁻	SS
Gviii	‘O’	RhD ⁻	AA
Gix	‘O’	RhD ⁻	AS
Gx	‘O’	RhD ⁻	AS

***Similar haemoglobin electrophoretic patterns were obtained with cow blood.**

Table 2. Blood group, rhesus factor and Hb genotype of sheep (*Ovis Aries dolrchr*). (Chuku and Uwakwe, 2012).

S.No	Blood group	Rhesus facors	Genotype
Si	'O'	RhD ⁻	AA
Sii	'O'	RhD ⁻	AA
Siii	'O'	RhD ⁻	AA
Siv	'O'	RhD ⁻	AA
Sv	'O'	RhD ⁻	AA
Svi	'O'	RhD ⁻	AA
Svii	'O'	RhD ⁻	AA
Sviii	'O'	RhD ⁻	AA
Six	'O'	RhD ⁻	AA
Sx	'O'	RhD ⁻	AA

Table 3: The Observed Haematological Parameters of Genotyping, Blood Groups, Rhesus Factor, Hb and G-S- T Activity of Catfish (Chuku and Uwakwe, 2012).

S/N. of fish	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9	Cat 10
Genot ype	AA									
Blood Group	A	O	O	AB						
Rhesu s Factor	D ⁻	D ⁻	D ⁻	D ⁺	D ⁻	D ⁻				
G-S-T activit y (IU)	11. 83	16. 27	15. 53	14. 79	18. 48	11. 46	14. 79	15. 53	14. 79	12. 94

- On exposure to 2% sodium metabisulphite, the RBC of catfish did not sickle.

Table 4: The observed haematological Parameters of Genotyping, Blood Groups, Rhesus Factor, Hb and G-S-T Activity of Mudskipper (Goby I) (Chuku and Uwakwe, 2012).

S/N. of fish	Ms k 1	Ms k 2	Ms k 3	Ms k 4	Ms k 5	Ms k 6	Ms k 7	Ms k 8	Ms k 9	Ms k 10
Genot ype	SS									
Blood Group	AB	AB	A	A	AB	AB	A	AB	AB	A
Rhesu s Factor	D ⁻	D ⁺	D ⁻	D ⁺	D ⁻	D ⁺				
G-S-T activit y (IU)	18.90	16.27	26.46	16.97	16.49	18.91	26.46	29.43	33.08	26.49
Hb (g/100 ml) of blood	5.57	2.36	3.15	3.07	1.18	5.57	3.157	3.54	3.15	2.36

Mean GST (\pm SD) = 14.64 \pm 2.11. Mean Hb (\pm SD) = 3.27 \pm 1.38

- On exposure to 2% sodium metabisulphite, the RBC of mudskipper sickled.

*Similar results were obtained for Goby II; all the samples tested gave HbSS electrophoretic pattern.

*Results for Tilapia: i).Hb concentration of Tilapia blood ranged from 3.79 - 12.94g/ml. Hb electrophoresis indicated a wider variability in Hb migration. Both HbSS, HbCC and HbCD electrophoretic patterns were identified. ii).Only the 'O' and 'AB' blood groups were identified. Both RhD⁺ and RhD⁻ were present.The GST activity of Tilapia blood samples ranged from 9.09-12.92 I.U. (Chuku and Uwakwe, 2010).

How is SCH inherited?

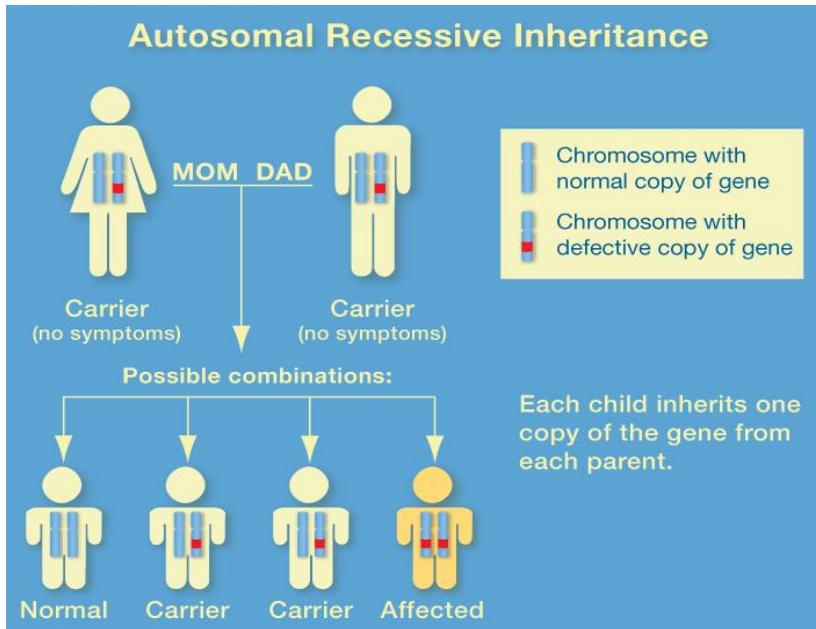


Figure 2. SCD inheritance pattern. (Wikipedia, the free encyclopedia, August, 2015)

Sickle cell disease is inherited in an autosomal recessive pattern. This means that a person inherits two abnormal copies of the haemoglobin gene, one from each parent. Several subtypes exist, depending on the exact mutation in each haemoglobin gene. A person with a single abnormal copy does not experience symptoms and is said to have sickle-cell trait.

Almost 300,000 children are born with a form of sickle-cell disease every year, mostly in sub-Saharan Africa, but also in other countries such as the West Indies and in people of African origin elsewhere in the world. The condition was first described in the medical literature by the American physician James B. Herrick in 1910, and in the 1940s and 1950s contributions by Nobel prize-winner Linus Pauling made it the first disease where the exact genetic and molecular defect was elucidated.

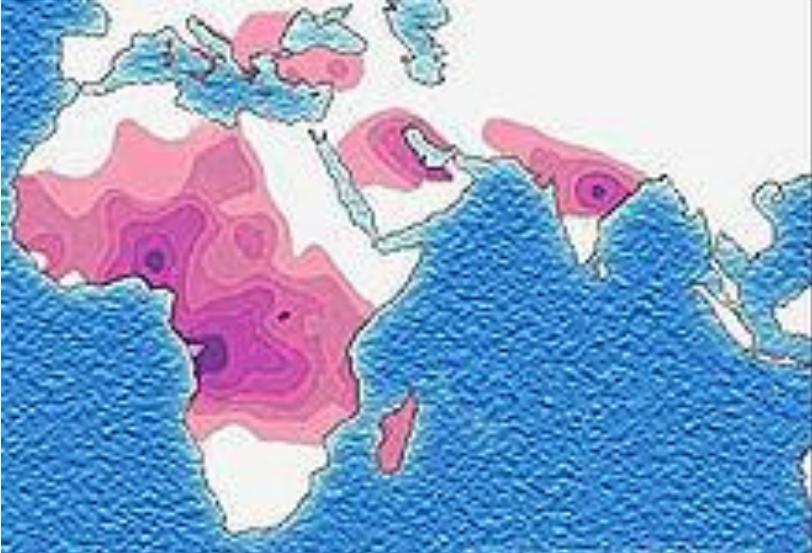


Figure 3. Distribution of the sickle-cell trait shown in pink and purple (Wikipedia, the free encyclopedia, August, 2015)



Figure 4. Historical distribution of malaria (no longer endemic in Europe) shown in green. (Wikipedia, the free encyclopedia, August, 2015)

Table 5: Significant cases of SCDs including thalassemias by continent/region.(Source: Ameh *et al.*2011)

Continent/region	Major disorder	Remark
Africa	(1) SCA (HbSS) (2) HbSC (3) α -Thalassemia HbC has lysine rather glutamine in 6th position as in β -globin of HbA	One in 12 Blacks worldwide carries the SCA trait. About 1 in 400 has SCA. About 75% of global SCAs are in Africa. About 1 0,000 SCA cases are born yearly in Nigeria. The carrier frequency ranges between 10% and 40% across equatorial Africa, decreasing to 1-2% in north Africa and <1% in South Africa.
Islands and countries in Mediterranean area and the Middle East	(1) HbS β^0 or β (2) α -Thalassemia (3) β -Thalassemia (4) HbC β^0 or β^+ (5) SC	These islands and countries including Turkey have significant cases of SCDs and thalassemias. Saudi Arabia has a yearly rate of ~3,000 newborns. Qatif City has the highest rate.
America—USA	(1) SCA (2) β -Thalassemia (3) HbC β^0 or β^+ (4) Other SC s	About 72,000 persons in the US have SCA, mostly African-Americans at the rate of 1 in 500 newborns as against 1 in 1, 200 for Hispanic-American births. In 2004, 83,149 cases of hospitalization were attributed to SCD in the US at a cost of ~\$488 million (Awasthy <i>et al.</i> , 2008).

Asia	<p>(1) SCA (2) α-thalassemia (3) β-thalassemia (4) $\text{HbC}\beta^0$ or β^+ (5) $\text{HbE}\beta^0$ or β^+ HbC has lysine rather than glutamine in 26th position as in β-globin of HbA</p>	<p>SCA is significantly prevalent in Bangladesh, China, and other Asian countries. In India the prevalence ranges from 9.4 to 22.2%. Hemoglobin thalassaemia is common in Cambodia, Thailand, and India. The Maldives has the highest incidence of thalassemsias in the world with a carrier rate of 18%. The corresponding figures for Bangladesh, China, India, Malaysia, and Pakistan range 3–8% of the populations.</p>
Europe	<p>(1) β-thalassaemia (2) α-thalassaemia (3) $\text{HbC}\beta^0$ or β^+ (4) $\text{HbE}\beta^0$ or β^+ (5) SCA</p>	<p>Aside from well-known cases in Italy, Greece, Portugal and Spain, significant prevalence of SCDs and the thalassemsias occur in others. In UK more than 200 babies are born annually with SCD. The highest prevalence of 1 in 2,415 is in France due to immigration from more endemic zones.</p>
<p>New SCDs/1000 in select areas: Nigeria: ≥ 19 Ghana: 10–18.9 S. Arabia: 5–9.9 Europe: ≤ 0.1</p>	<p>Types of SCD seen: (1) β-thalassaemia (2) α-thalassaemia (3) $\text{HbC}\beta^0$ or β^+ (4) $\text{HbE}\beta^0$ or β^+ (5) SCA</p>	<p>New SCDs/1,000 in selected areas: Mexico: 0.1–0.19 Central America: 1–18.9 South America: 0.1–4.0 Southeast Asia: 0.2–18.9 Oceania: ≤ 0.1</p>

What are the symptoms of sickle cell disease?

Sickle cell disease prevents oxygen from effectively reaching the spleen, liver, kidneys, lungs, heart, or other organs, causing a lot of damage. Without adequate oxygen supply, the integrity of these cells that make up these organs are greatly compromised leading to damage/cell death. For example, the spleen is often destroyed in these patients, leading to some loss of immune function. As a result, these patients often experience frequent infections.

The red blood cells of patients with sickle cell disease don't live as long as healthy red blood cells. So people with this disorder often have low red blood cell counts (anemia), which is why this disease is commonly referred to as sickle cell anemia.

When sickle-shaped red blood cells get stuck in blood vessels, patients can have episodes of pain called crises. Other symptoms include delayed growth, strokes, and jaundice (yellowish skin and eyes because of liver damage).

Organ damage and other complications often shorten patients' lives by about 30 years.

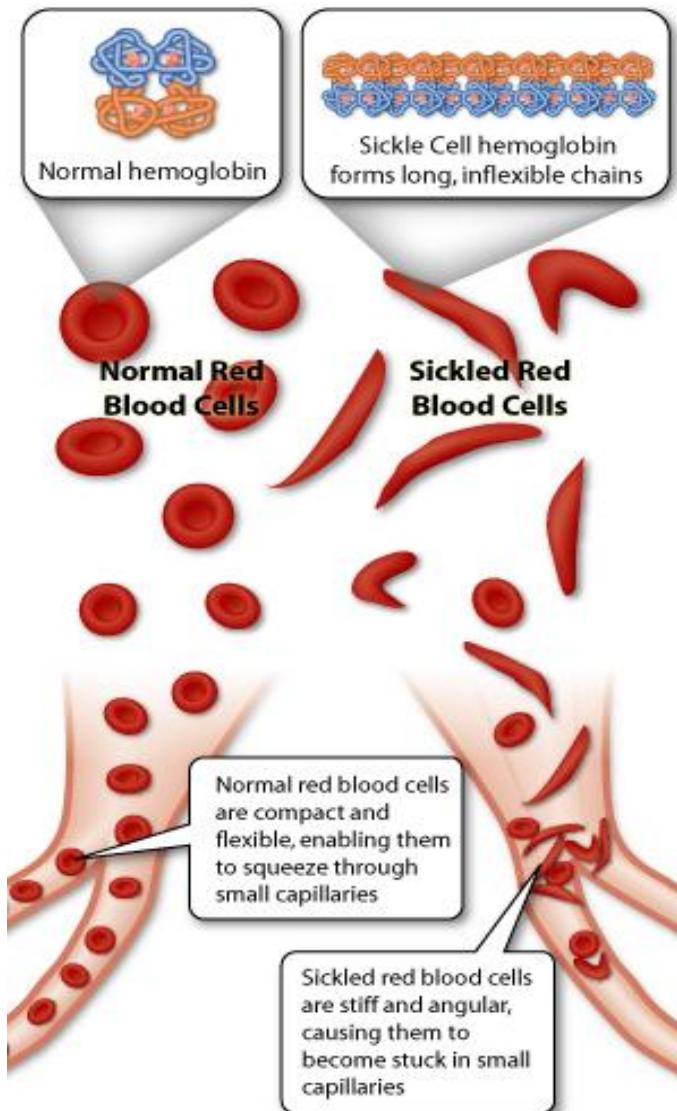


Figure 5. Vaso-occlusion by HbS erythrocytes (Wikipedia, the free encyclopedia, August, 2015)

Sickle-cell crisis

The term "sickle-cell crisis" or "sickling crisis" may be used to describe several independent acute conditions occurring in patients with SCD. SCD results in anemia and crises that could be of many types including the vaso-occlusive crisis, aplastic crisis, sequestration crisis, haemolytic crisis, and others. Most episodes of sickle-cell crises last between five and seven days (Best bets, 2010). "Although infection, dehydration, and acidosis (all of which favor sickling) can act as triggers, in most instances, no predisposing cause is identified (Kumar *et al.* 2009).

Vaso-occlusive crisis

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ resulting in ischaemia, pain, necrosis, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration, analgesics, and blood transfusion; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Vaso-occlusive crisis involving organs such as the penis (Olujohungbe, 2013) or lungs are considered an emergency and treated with red-blood cell transfusions. Incentive spirometry, a technique to encourage deep breathing to minimise the development of atelectasis, is recommended (Glassberg, 2011).

Splenic sequestration crisis

Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected (Anie and Green, 2012). It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anemia. This autosplenectomy increases the risk of infection from encapsulated organisms;(Pearson.1977, Wong *et. al.* 1992) preventive antibiotics and vaccinations are recommended for those with such asplenia.

Splenic sequestration crises are acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in hemoglobin levels with the potential for hypovolemic shock. Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion. These crises are transient, they continue for 3–4 hours and may last for one day (Khatib *et.al.* 2009).

Acute chest syndrome

Acute chest syndrome (ACS) is defined by at least two of the following signs or symptoms: chest pain, fever, pulmonary infiltrate or focal abnormality, respiratory symptoms, or hypoxemia (Glassberg,2011). It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD, majority of cases present with vaso-occlusive crises then they develop ACS (Mekontso *et. al.* 2008, Paul *et. al.*,2011). Nevertheless, about 80% of patients have vaso-occlusive crises during ACS.

Aplastic crisis

Aplastic crises are acute worsenings of the patient's baseline anaemia, producing pallor, tachycardia, and fatigue. This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and destroying them (Kumar *et. al.*, 2009). Parvovirus infection nearly completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of SCD patients results in an abrupt, life-threatening situation. Reticulocyte counts drop dramatically during the disease (causing reticulocytopenia), and the rapid turnover of red cells leads to the drop in haemoglobin. This crisis takes 4 days to one week to disappear. Most patients can be managed supportively; some need blood transfusion (Slavov *et. al.*, 2011).

Haemolytic crisis

Haemolytic crises are acute accelerated drops in haemoglobin level. The red blood cells break down at a faster rate. This is particularly common in patients with coexistent G6PD deficiency (Balgir, 2012). Management is supportive, sometimes with blood transfusions.

Other recognized crisis

One of the earliest clinical manifestations is dactylitis, presenting as early as six months of age, and may occur in children with sickle-cell trait (Jadavji and Prober, 1985). The crisis can last up to a month (Worrall and Butera, 1976).

Complications of SCH

Sickle-cell haemoglobinopathy can lead to various complications, including:

- Increased risk of severe bacterial infections due to loss of functioning spleen tissue (and comparable to the risk of infections after having the spleen removed surgically). These infections are typically caused by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists continuing treatment indefinitely. Patients benefit today from routine vaccination for *S. pneumoniae* (Kavanagh *et. al.*, 2011).
- Stroke, which can result from a progressive narrowing of blood vessels, prevents oxygen from reaching the brain. Cerebral infarction occurs in children and cerebral haemorrhage in adults.
- Silent stroke causes no immediate symptoms, but is associated with damage to the brain. Silent stroke is probably five times as common as symptomatic stroke. About 10–15% of children with SCD suffer strokes, with silent strokes predominating in the younger patients (Adams *et. al.*, 2001, Adams, 2007).
- Cholelithiasis (gallstones) and cholecystitis may result from excessive bilirubin production and precipitation due to prolonged haemolysis.

- Avascular necrosis (aseptic bone necrosis) of the hip and other major joints may occur as a result of ischaemia (Marti-Carvajal *et. al.* 2004).
- Decreased immune reactions due to hyposplenism (malfunctioning of the spleen) (Kenny *et. al.* 1980).
- Priapism and infarction of the penis (Chrouser *et. al.* 2011).
- Osteomyelitis (bacterial bone infection), the most common cause of osteomyelitis in SCD is *Salmonella* (especially the atypical serotypes *Salmonella typhimurium*, *Salmonella enteritidis*, *Salmonella choleraesuis* and *Salmonella paratyphi B*), followed by *Staphylococcus aureus* and Gram-negative enteric bacilli perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction (Almeida and Roberts, 2005).
- Opioid tolerance can occur as a normal, physiologic response to the therapeutic use of opiates. Addiction to opiates occurs no more commonly among individuals with sickle-cell disease than among other individuals treated with opiates for other reasons.
- Acute papillary necrosis in the kidneys
- Leg ulcers (Rudge, 1991).
- In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages, and retinal detachments can lead to blindness (Elagouz *et. al.* 2010). Regular annual eye checks are recommended.
- During pregnancy, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia
- Chronic pain: Even in the absence of acute vaso-occlusive pain, many patients have unreported chronic pain (Smith *et. al.* 2008). Pulmonary hypertension (increased pressure on the pulmonary artery) can lead to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance, and episodes of syncope (Gladwin *et. al.* 2004).
- Chronic renal failure due to sickle-cell nephropathy manifests itself with hypertension, protein loss in the urine, loss of red blood cells in urine and worsened anaemia. If it progresses to end-stage renal failure, it carries a poor prognosis (Powars *et al.* 1991).

POSSIBLE TRIGGERS OR INHIBITORS OF HBS GELATION AND/OR ERYTHROCYTE SICKLING: OUR FINDINGS

A: SOME HAEMOGLOBIN-S POLYMERIZATION ENHANCERS

1. Superoxides.--- Anosike *et.al.* 1991, Uwakwe *et.al.* 1998, 1999
2. Haemin – Anosike *et.al.* 1991, Uwakwe *et.al.* 1998, 1999.
3. Methaemoglobin(Fe^{3+}).----- Anosike *et.al.* 1991, Uwakwe *et.al.* 1998, 1999
4. Quinine and its Congeners (Chloroquine, Camoquine(Amodiaquine) Mefloquine (Lariam), Nivaquine, Piperaquine, etc).– Uwakwe and Akhidue 2000, Ayalogu *et. al.*, 2000, Uwakwe and Ononiwu 2003, chikezie *et.al.* 2008, 2009, 2010.
5. Cyanide – Uwakwe *et.al.* 1991.
6. Caffeine (1,2,4,6 tetraoxypyrimidine) – Uwakwe *et.al.* 2002, Spiff and Uwakwe, 2003., Uwakwe and Ugwu (2003) NSBMB abstract.
7. Hypoglycemic drugs: Daonil (A glibenclamide), Glucophage (A metformin), Diabinese (A sulphonil urea) and Glucobay.– Uwakwe and Bob manuel (2003) NSBMB, Ibekwe *et al.* 2008, Onuoha *et al.* 2007, 2012,.
8. Zidovudine (Anti-retroviral drug)-Okonkwo and Uwakwe, 2013.
9. Nevirapine and Efavirenzin (Anti-hypertensives) – Uwakwe, Wodu and Monanu 2015.
10. Ethanol.-----Uwakwe *et.al.*, 2002
11. Sodium benzoate.....Ibekwe *et al.* , 2008

These enhance HbS gelation/Sickling rate and in some cases Osmotic Fragility also.

B: SOME HAEMOGLOBIN POLYMERIZATION INHIBITORS

1. Nicotinic acid (Pyridine beta carboxylic acid, Niacin, Vitamin B_6)– Uwakwe and Onyeike 2003.
2. Glutamic acid (As Monosodium glutamate). ---Uwakwe and Nwinuka, 2000.

3. Vitamin C (Ascorbic acid). -----Ekeke *et. al.* 2001.
4. Aspirin and Paracetamol – Uwakwe and Akhidue 2000 Thiamin (Vitamin B1).----- Uwakwe and Akhidue 2000
ETC

C: COMPOUNDS PRODUCING NO SIGNIFICANT EFFECT ON HAEMOGLOBIN-S POLYMERIZATION

1. Halofantrine (Halfan)-- Uwakwe and Ononiwu 2003
2. Fansida(Suphadoxine/Pyrimethamine combination)-----
Ayalogu *et al.* 2000, Uwakwe and Ononiwu 2003.,
3. Certain antibiotics (Ampicilin, Tetracycline and Chloramphenicol)– Uwakwe and Nkpa (2003)
ETC

Management of SCH

A: CLASSICAL APPROACH

Folic acid and penicillin

1 mg dose of folic acid daily for life. From birth to five years of age, they will also have to take penicillin daily due to the immature immune system that makes them more prone to early childhood illnesses.

Malaria chemoprophylaxis

The most common cause of painful crises in malarial countries is infection with malaria. It has therefore been recommended that people with sickle-cell disease living in malarial countries should receive anti-malarial chemoprophylaxis for life.

Vaso-occlusive crisis

Most people with sickle-cell disease have intensely painful episodes called vaso-occlusive crises. The frequency, severity, and duration of these crises, however, vary tremendously. Painful crises are treated symptomatically with analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients

require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is also an effective agent that is frequently prescribed by doctors in order to help control any itching associated with the use of opioids.

Acute chest crisis

Management is similar to that of vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since cell wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome), oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the patient's red cell mass for normal red cells, which decreases the percent of haemoglobin S in the patient's blood.

Hydroxyurea

Hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 (Charache *et al.*) and shown to possibly increase survival time in a study in 2003 (Steinberg *et al.*). This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.

Transfusion therapy

Blood transfusions are often used in the management of sickle-cell disease in acute cases and to prevent complications by decreasing the number of red blood cells (RBC) that can sickle by adding normal red blood cells.

Bone marrow transplants

Bone marrow transplants have proven to be effective in children. Bone marrow transplants are the only known cure for SCD.

However, bone marrow transplants are difficult to obtain because of the specific Human Leucocyte Antigen (HLA) typing necessary. Ideally, a twin family member (syngeneic) or close relative (allogeneic) would donate the bone marrow necessary for transplantation.

B: NON CLASSICAL OR NATURAL APPROACHES TO SCH MANAGEMENT AND/OR PREVENTION

1. Genetic Counselling

Application of the principle of Mendel’s theory.

As much as possible, **AS** individuals should not intermarry.

Also, **AS** individuals should not marry **SS** individuals and **SS** individuals should not intermarry.

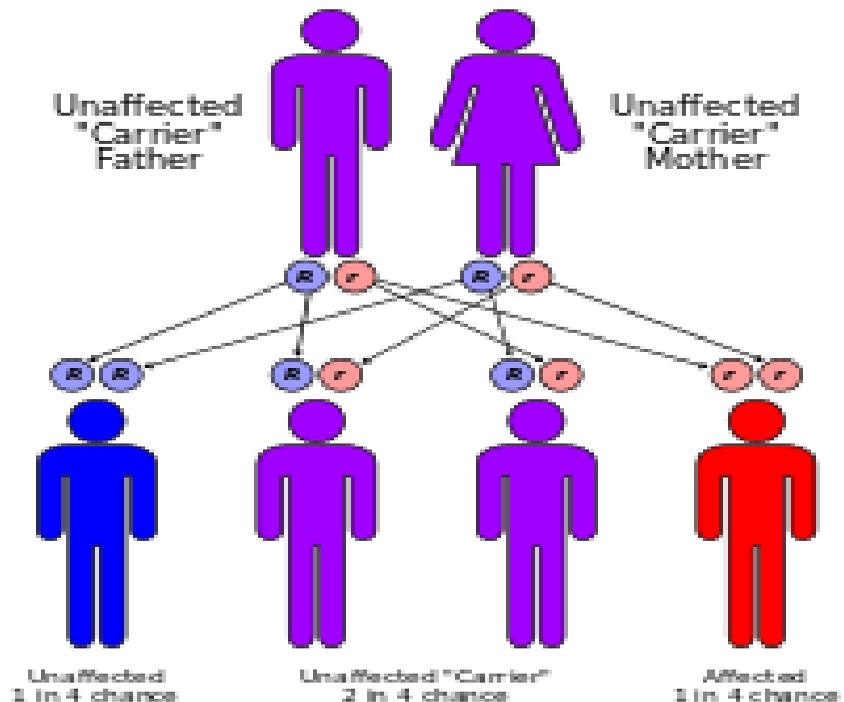


Figure 6. SCD inheritance pattern

2. Herbal remedies

Patients in West Africa where sickle cell anemia (SCA) is endemic have for ages been treated with natural products, especially herbs, as, is still the case in rural communities. According to Ameh *et al.* (2012), antisickling herbs abound in West Africa and the most promising may yet be found. In their report, they presented what they captioned manifestations of SCA and strategies for management including herbal treatment as shown

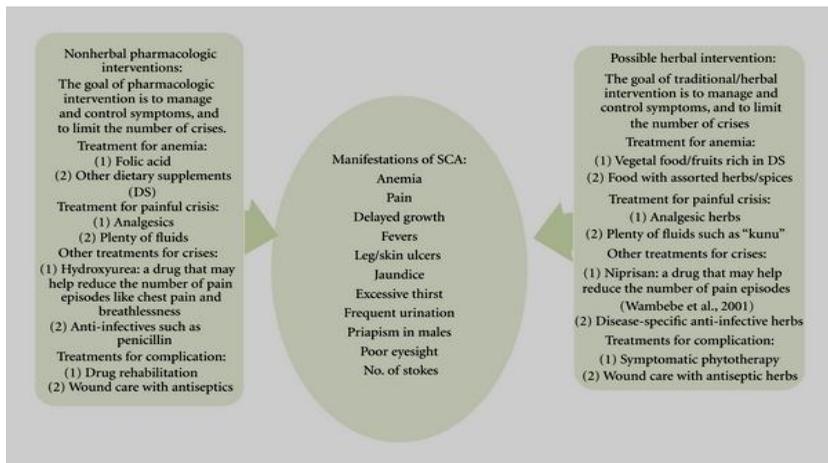


Figure 7. Herbal versus Non-herbal interventions in SCD management (Ameh *et al.*2012)

Traditional Herbal Approaches to Sickle Cell Anemia in Nigeria

It has variously been reported that among the Efik and Ibibio, Hausa, Igbo, Idoma, and Yoruba: clove (*Eugenia caryophyllata* or “kanunfari” in Hausa; *Piper guineense* (“eche” in Idoma or “akwa-ose” in Igbo); grains of paradise (*Aframomum melegueta* or “otuta” in Idoma); Sorghum bicolor; *Pterocarpus osun* (common in the Yoruba state of Osun) are used in various health conditions, including sickle cell anemia.

E. caryophyllata, *P. guineense*, *P. osun*, and *S. bicolor* are the herbal components of the Yoruba recipe upon which the antisickling drug

Niprisan is based. Prior to the era of Niprisan these herbs were either extracted with “ogogoro” (ethanolic distillate of palm wine) or with an aqueous solution trona (sodium sesquicarbonate—a mineral used in Nigeria as tenderizer). Niprisan has passed phases IIA and IIB of the US FDA test, and is widely used in Nigeria, and is also known in India and the USA.

It has been suggested by Ameh *et al.*(2011) that phytocannabinoids and vanilloids in *E. caryophyllata* and *P. guineense* may account for some of the useful effects of Niprisan in sickle cell crisis. Some of these compounds, including shikimic acid derivatives (vanilloids) and cannabinoids are indicated in Figure 8 and Table 2, respectively.

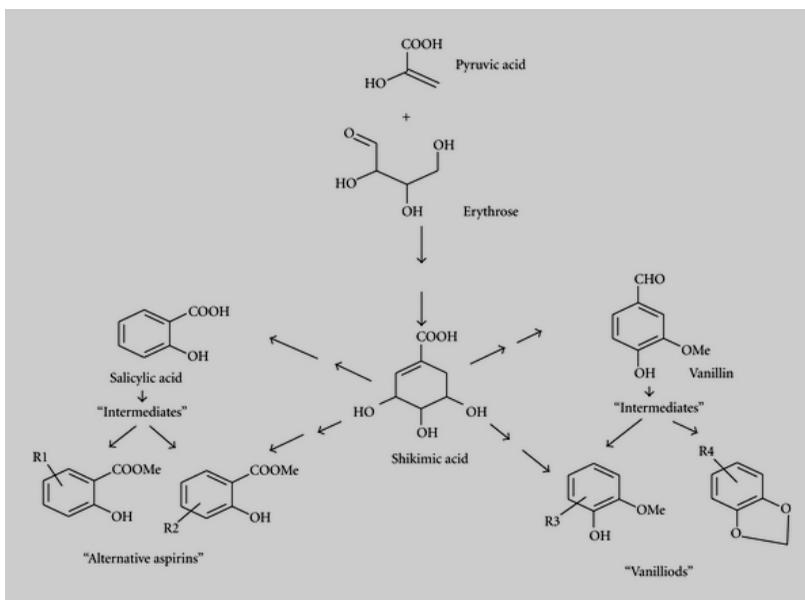
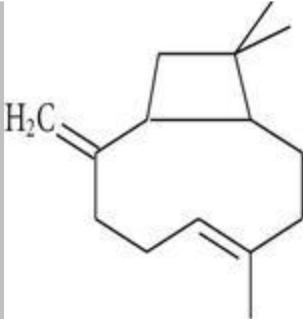


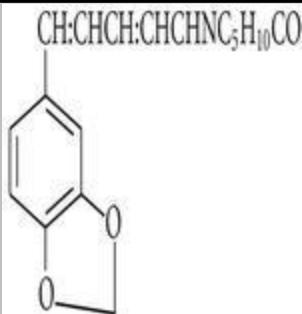
Figure 8: Biosynthesis and relationship of shikimic acid to “alternative aspirins” and “vanilloids”.

The shikimic acid pathway is a key biosynthetic pathway for several phytochemicals known for their medicinal attributes. The

Figure illustrates the biosynthesis of shikimic acid from pyruvic acid and erythrose and the relationship between the acid and its byproducts and intermediates, some of which possess aspirin-like effects, like analgesia and desickling of sickled RBCs. Such byproducts/intermediates include salicyclic acid derivatives, vanillin, piperine, capsaicin, and cubebin. Piperine, capsaicin, and cubebin as byproducts of shikimic acid are the likely antisickling agents in Niprisan. It is of note that Sofowara [1979] had attributed the antisickling properties of *Fagara zanthoxyloides* to divanilloylquinic acids.

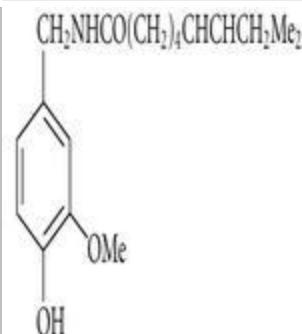
Table 6: Some bioactive agents of *P. guineense* and *E. caryophyllata*—components of Niprisan. (Ameh *et al.* 2012)

Constituent	Chemistry and pharmacology
 <p data-bbox="227 1042 393 1082">Caryophyllene</p>	<p data-bbox="477 687 972 919">β-Caryophyllene is a warm constituent of <i>P. guineense</i>, found also in <i>C. sativa</i> and clove. It occurs as a mixture with α-caryophyllene. It has been found to bind selectively to cannabinoid receptor type 2. This is a key finding given the role of this receptor in pain control.</p>



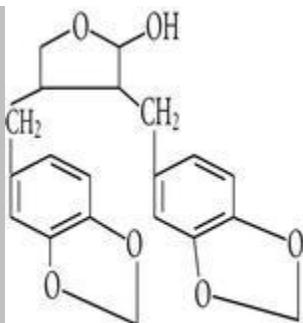
Piperine-a vanilloid

Piperine and chavicine are geometric isomers responsible for the pungency of *P. guineense*, constitute ~5–8%, and are used as ethnomedicines.



Capsaicin-a vanilloid

Capsaicin is (8-methyl-N-vanillyl-6-nonenamide) a pungent constituent that produces a burning-sensation in all tissues. Capsaicin and related compounds are called capsaicinoids or vanilloids.



Cubebin

Cubebin is tetrahydrodiperonyl-2-furanol. The furanyl and piperonyl (or vanilyl) groups draw attention to the palliate roles of furan and vanilloids in SCD crisis. “Cubebine” is French designation for diethylether extract of *P. cubeba*.

Vanilloids and Cannabinoids are agents in Pain Control. The vanilloids, namely: vanillin, eugenol, zingerone, capsaicin, and piperine (isomer of capsaicin), are molecules with distinctive flavours, yet are quite similar in their molecular structures. All contain a benzene ring. Subtle changes in the sizes or positions of groups of atoms attached to the ring dramatically change their organoleptic and other physicochemical characteristics. Eugenol, capsaicin, and piperine are present in *E. caryophyllata* and *P. guineense* and are responsible for their analgesic potentials.

SOME HERBAL MATERIALS USED IN MANAGING SCA

A summary of the gross effects and the proposed general actions of some of the herbs used in SCA treatment is presented in Table 3.

Table 7: Herbal materials used in managing SCA and their probable mode of action.(Ameh *et al.* 2012)

Herb	Probable general effect/mode of action/phytochemical constituents
<i>Fagara zanthoxyloides</i> (root)	Three isomeric divanilloylquinic acids (burkinabin A, burkinabin B, and burkinabin C) were identified as the likely antisickling agents. But some workers have proposed coumarins, vanillic acid, parahydroxybenzoic acid, and paraflurobenzoic acid (Sofowara and Isaacs, 1971, Sofowara, 1979).
<i>Carica papaya</i>— (unripe fruit or leaf)	Antisickling effects of 87% inhibitory and 74% reversal activities were obtained from the 5-day fermentation of unripe fruit of <i>C. papaya</i> at 2.5 mg per mL of water. Methanol extract had 64% inhibitory and 55% reversal activities while the chloroform extract was inactive. Phenylalanine, tyrosine, and glycine were thought to be responsible (Thomas and Ajani, 1987, Ogunyemi <i>et al.</i> , 2008, Imaga <i>et al.</i> , 2009).
Garlic (bulb)	The basis is unknown, but garlic is used in many infective conditions especially respiratory infections in SCA (Ohnishi <i>et al.</i> , 2000).

<i>Hymenocardia acida</i> (leaf)	Mpiana <i>et al.</i> (2009) related the anti-SCA activities of <i>H. acida</i> to anthocyanins.
<i>Cajanus cajan</i> (seed)	Phenylalanine is thought to be the most active principle in <i>Cajanus cajan</i> seed—a component of Ciklavit antisickling phytomedicine, developed in Nigeria by Professor, Ekeke (Ekeke and Shode, 1992, Akinsulie <i>et al.</i> , 2005).
<i>Khaya senegalensis</i> (stem bark/leaf)	Fall <i>et al.</i> (1999) attributed the anti-SCA effects of <i>K. senegalensis</i> to limonoids.
The herbs Niprisan: (1) <i>S. bicolor</i> (2) <i>P. osun</i> (3) Clove (4) <i>P. guineense</i>	The bases for the actions of <i>Sorghum bicolor</i> and <i>Pterocarpus osun</i> are unknown, but they are rich in brightly coloured red/orange flavonoids. They probably act as hematonics especially if they contain folic acid or its analogues. Given their blood red colour, the “Doctrine of Signatures” may have influenced their inclusion by Yoruba sages of old. It had been supposed that the principles in Niprisan that mitigate, palliate, or reduce the frequency of SCA crisis probably reside mainly in clove and <i>P. guineense</i> (Ameh <i>et al.</i> 2011, 2012, Mojisola <i>et al.</i> , 2009, Awodogan <i>et al.</i> , 1996, Gamaniel <i>et al.</i> ,1998, Obozie <i>et al.</i> , 2010).

Clove is *Eugenia caryophyllata*, which, like *P. guineense*, contains principles that impact SCA crisis. Notably, the isomeric divanilloylquinic acids of *Fagara zanthoxyloides* contain the vanillyl group as do the vanilloids of clove and *P. guineense*.

BIOCHEMICAL BASIS FOR HERBAL MANAGEMENT OF SCA

Structure of Hemoglobin in Relation to Antisickling Agents

Hemoglobins exist in two quaternary states—the deoxygenated conformation called Tense or T-state and the oxygenated conformation called Relaxed or R-state. Sickling occurs only in T-state haemoglobin S (HbS) due to its polymerizing tendency. Thus, a key approach to the crisis of sickling lies in finding a means of inhibiting this tendency of T-state HbS or of causing it to revert to the R state. Safo and coworkers (Safo *et al.* 2004) had shown that

both HbA and HbS possess allosteric sites with which suitable chemical ligands can interact to shift the equilibrium in favor of the R state and have identified several such entities, called allosteric regulators. These regulators in the case of HbS act as antisickling agents—which can be defined as entities that can inhibit or reverse the sequence of pathological processes leading to sickling. Compounds known to possess this type of effect include (i) “alternative aspirins” such as acetyl-3,5-dibromosalicylic acid (Safo *et al.* 2004), (ii) furfural derivatives (Safo *et al.* 2004), and (iii) a variety of compounds called capsaicinoids or vanilloids that possess a vanilyl functional group, or its approximation as in vanillin or related compounds (Walder *et al.*, 1977). These vanilloids include some substituted benzaldehydes (Abraham *et al.*, 19991) and several shikimic acid byproducts. The structures of some of these antisickling entities including the “alternative aspirins” and “vanilloids” were shown in Figure 8

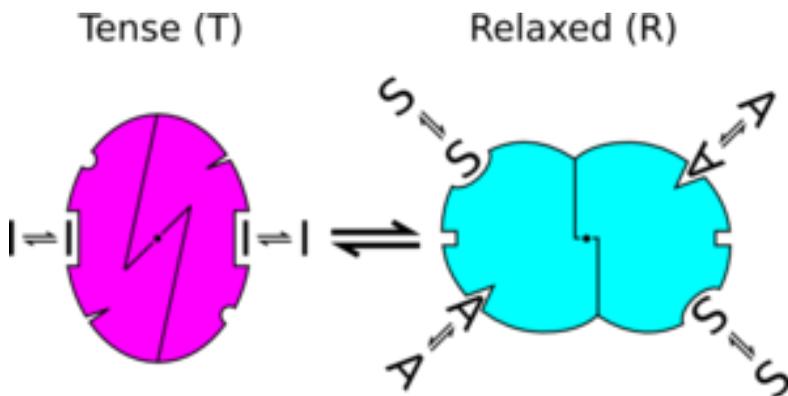


Figure 9: An allosteric transition of a protein between R and T states stabilised by an **Agonist**, an **Inhibitor** and a **Substrate**.

SOME OTHER PLANTS/PLANT MATERIALS WITH ANTI SICKLING POTENTIALS: OUR FINDINGS

1. *Cyperus esculentus*-----*Monago and Uwakwe, 2009*
 2. *Monodora miristica*- -----*Uwakwe and Nwaoguikpe, 2008*
 3. *Xylopia aethiopica*-----*Uwakwe and Nwaoguikpe, 2008*
 4. *Garcinia kola*-----*Adelodu, 2010*
 5. *Zingiber officinale*-----*Uwakwe and Bresimo, 1999*
 6. *Afromenum miliquet*----- *Uwakwe and Bresimo, 1999*
 7. *Cymbopogon citractus*-----*Uwakwe and Eze, 2000*
 8. *Talinum triangulare*-----*Uwakwe and Eze, 2000*
 9. *Moringa oleifera*-----*Uwakwe and Eze, 2000*
 10. *Ocimum canum*-----*Uwakwe and Eze,2000*
 11. *Ocimum gratissimum*-----*Uwakwe and Eze, 2000*
 12. *Aloe perfoliata L. var. vera*----*Uwakwe and Offonze, 2003*
 13. *IAA*-----*Uwakwe, Ayalogu and Wegwu, 2003*
 14. *Anacardium occidentale*----*Chikezie and Uwakwe, 2011*
 15. *Psidium guajava*----- *Chikezie and Uwakwe, 2011*
 16. *Terminalia catappa*----- *Chikezie and Uwakwe, 2011*
 17. *Stenostylic stenocarpa*----*Ekeke, Uwakwe and Nwaoguikpe,2001*
 18. *Derris macrophylla*----- *Ekeke, Uwakwe and Nwaoguikpe,2001*
 19. *Vigna unguiculata*----- *Ekeke, Uwakwe and Nwaoguikpe,2001*
 20. *Kapanji*----- *Ekeke, Uwakwe and Nwaoguikpe,2001*
 21. *Lycopersicum esculentum*--*Ekeke, Uwakwe and Nwaoguikpe, 2001*
 22. *Ananas comosus*----- *Ekeke, Uwakwe and Nwaoguikpe, 2001*
 23. *Mangifera indica*---*Ekeke, Uwakwe and Nwaoguikpe,2001*
 24. *Citrus sinensis*---- *Ekeke, Uwakwe and Nwaoguikpe,2001*
 25. *Citrus paradise*--- *Ekeke, Uwakwe and Nwaoguikpe,2001.*
 26. *Carica papaya*---- *Ekeke, Uwakwe and Nwaoguikpe,2001.*
 27. *Syzygium jambos*-- *Ekeke, Uwakwe and Nwaoguikpe,2001.*
 28. *Citrus limon*---- *Ekeke, Uwakwe and Nwaoguikpe,2001.*
- ETC.**

Gabriel Ekeke Centre for Sickle Cell Research is currently investigating over 100 plant species for possible antisickling activity. The centre hopes to come up with more potent antisickling

formulations for the management of SCD. We need every encouragement to achieve this goal.

MANAGEMENT OF SCH: WHICH WAY FORWARD?

- Every possible solution should be exploited for maximum benefits. While hoping for an ultimate classical solution, we should not disregard possible solutions from our natural environment. The possibilities provided by our natural herbs are quite enormous and should be exploited to the fullest for the management of SCD and other pathologies.
- Pharmacists and Nutritionists should always consider HBS subjects in drug and food formulations and testing.
- Furthermore, there is every need to bridge the gap between our traditional herbal medical practice and scientific research.
- It must also be stated that governments, corporate organizations and philanthropic individuals should not shy away but rather be more proactive in funding research activities which are geared towards solving the problems of our immediate environment and citizenry.

MANY THANKS FOR LISTENING!

A.A.UWAKWE

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Citation on Prof. A. A. Uwakwe



Prof. Augustine Amadikwa Uwakwe was born in 1962 to Mr. and Mrs. Francis Uwakwe of Ikeduru, Imo State, Nigeria. He started his primary education in 1970 after the Nigerian civil war.

Prof. Uwakwe obtained his B.Sc, M.Sc and PhD degrees in Biochemistry from the University of Port Harcourt. He was the best graduating student of his B.Sc class and the first PhD product of his department. He started his lecturing career in 1991 as an Assistant Lecturer in Biochemistry. He became an Associate Prof. in 2005 and a full Professor of Biochemistry in 2009. His major research interests are in: Medical Biochemistry, Enzymology and Biochemical Pharmacology. He has over 160 research publications (national and international) in the areas of phytomedicine, blood diseases, enzymology and general biochemistry.

Prof. A. A. Uwakwe has served different Universities in several capacities such as Coordinator of several programmes, member and Chairman of several University Committees, Head of Department, Director of Research Centre, External Examiner for Undergraduate, Postgraduate and MBBS programmes, visiting Professor, External

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Prof. Uwakwe is a **Fellow of the Strategic Institute for Human Resources and National Development**, and also a **Fellow of the Nigerian Society of Biochemistry and Molecular Biology (NSBMB)**. He has been a **member, Research Board of Advisors, of the American Biographical Society (ABS)** from 2006 to date. He is also a **Consulting editor** of the Contemporary **‘Who is Who’** a publication of ABS. Professor Uwakwe is a member of several national and international Professional Organizations.

He is a founding member and current **Chairman, Board of Trustees of Sickle Cell Research and Awareness Group (SCRAG)**. He is also founding member and **Chairman, Board of Trustees, of West African Society for Sickle Cell Research, Awareness and Control (WASRAC)**.

Prof. A. A. Uwakwe is happily married to Mrs. Theresa N. Uwakwe (an Accountant) and their marriage is blessed with five (5) children (one (1) Girl and four (4) Boys).

Vice Chancellor, Sir, I present to you, a humble and God-fearing Academic, to present the 132nd inaugural lecture of University of Port Harcourt; I present to you, Professor Augustine Amadikwa Uwakwe.

Professor G. C. Obute
University Orator