Sickle cell disease is a genetic disorders characterized by chronic haemolytic anaemia due to adverse effects of oxygen transport by the red blood cells. This leads to a decrease in oxygen supply to peripheral tissues. Because of the reduced oxygen tension, the red blood cells become sickle shape and sticky under condition of hypoxia, dehydration or acidosis. These sickled red blood cells clump inside large and small blood vessels leading to ischemia, pain and infarction. The pathogenesis of SCD is due mainly to polymerization of sickle red blood cells causing chronic haemolytic anaemia, vasoocclusive crisis and intravascular haemolysis. In this regard, many workers have reported their noteworthy contributions as:


Brugnara C.et al (2000) reported that, Oxidative damage to cells is believed to be responsible for the activation of KCL-cotransport in sickled erythrocytes. Sickle cell erythrocytes are fragile and dehydrated and it is important that minerals and anti–oxidants are constantly supplied to maintain hydration and membrane integrity.
Benerjee et al (2001) noted that the clinical spectrum of sickle cell disease ranges from mild liver function test abnormalities in asymptomatic patients, to dramatic clinical crises with marked hyperbilirubinemia and liver failure. The study also reported that the patients with sickle cell anemia have hyperzincuria and systemic zinc deficiency.

Mutay Aslan et al (2001) reported that the episode of hypoxia–reoxygenation associated with SCD leads to the release of xantine oxidase into the circulation from hepatic cell replete in the activity of this source of $O_2^-$ and $H_2O_2$. This significantly contributes to the vascular disease that is the hallmark of sickle cell anemia.

Nath et al (2001) suggested that alterations in cellular redox occur in the sickle kidney. These redox alterations are countered by the induction of HO-1, a system that, quite remarkably, possesses attributes that may oppose many of the pathogenetic mechanisms underlying renal and other complications of sickle cell disease.

Elizabeth S Klings et al (2001) concluded that Reactive oxygen species may play an important role in the vascular dysfunction that is observed during ACS and VOC of SCD.

Elizabeth m barden et al (2002) summarised that Children with SCD have impaired growth, delayed puberty, and poor nutritional status.
S Richard et al (2002) demonstrated that the majority of patients with sickle cell disease have normal liver function as measured by standard biochemical parameters, despite transfusion and exposure to transfusion transmitted viruses.

Viktória Jeney et al (2002) suggested that heme derived from free Hb in plasma may threaten vascular endothelial cell integrity via oxidative modification of LDL this lipoprotein, in turn, induces the cytoprotectants heme oxygenase and Ferritin.

A V. Shrikhande et al (2003) reported that no significant correlation was found between HbF and total hemoglobin. The study showed that both the sexes are have more or less similar and higher HbF levels but total haemoglobin is low in females as compared to males.

Jyoti Titus et al (2004) concluded that it is clearly evident that both homozygous as well as heterozygous patients are exposed to enhanced oxidative stress as compared to controls. It is also evident that the antioxidant system is imbalanced in these patients and is probably unable to effectively counteract the augmented oxidative stress.

Saika S. Somjee et al (2004) summarised in their study that high circulating AGE levels in patients with SCA suggest that AGEs have a role in the vascular pathology of the disease. Further they suggested that AGEs could also have a role in the acute vascular pathology of SCA.
Anil Pathare et al (2004) reported that sickle cell from Oman showed a significant elevation in IL-1β, INF-γ and IL-6 in steady state, when compared to normal controls.

Malaria appears to have played a role in precipitating some of the hyperhaemolytic episodes. The authors have further studied to elucidate this role are required so that appropriate recommendations regarding malaria prophylaxis can be made in patients with sickle cell anemia. A. I. Juwah et al (2004)

Joan L et al (2004) found that the alteration in vitamin A, Hb%, hematocrit, and BMI in their study.

Filiz Şimşek et al (2005) concluded that SOD (a preventive antioxidant) values and plasma MDA (the breakdown product of lipid peroxidation) levels were found to be higher in beta-thalassemic patients than healthy children, and suggested that The administration of selective antioxidants such as vitamin E with an appropriate diet or appropriate treatment might represent a promising way of counteracting with the oxidative damage and its deleterious effects on the progression of the disease.

Claudia R. Morris et al (2005) observed that dysregulated arginine metabolism is associated with intravascular hemolysis, inflammation, and endothelial cell activation. Alterations in the normal balance of arginine and
its catabolic byproducts ornithine, citrulline and proline are associated with pulmonary hypertension and prospective risk of death.

Yoshihito Iuchi et al (2005) studied that anemia is caused by oxidative stress, have implicated oxidative stress in anemia complicated with some infectious diseases. For example, malaria infection results in decreased antioxidant enzymes and substances such as catalase, GPx, SOD, GSH, ascorbate, and plasma tocopherol. The development of new antioxidant drugs with a function based on ROS reduction might constitute a promising tool not only for hereditary anemia but also for the control of the infection-mediated anemia.

Taiwo Kotila et al (2005) reported that the minimal elevation of the transaminases which is not gender or age dependent were observed in steady state sickle cell disease, higher levels of alkaline phosphatase may be due to associated vasoocclusive crises involving the bones rather than a pathology of liver.

Switzer, J.A. et al (2006) suggested that oxidants and cytokines result in up regulation of endothelial adhesion molecules and increased sickle cell adhesion.

Kaul, D.K. et al (2006) summarized in their study that the reactive oxygen species induced by reperfusion can react with nitric oxide to form the toxic peroxynitrite radical, increasing vasomotor tone. In an ex-vivo study in
the rat mesocecal vasculature, PAF induced sickle cell adhesion was reduced by antioxidants.

**R marouf et al (2006)** concluded in their study that Evaluation of renal function is essential in patients with SCD. The unreliability of the ubiquitously used creatinine makes the assessment of GFR in patients with SCD difficult in clinical practice and estimates derived from cystatin C could replace creatinine based methods for routine assessment of renal function in patients with SCD.

**Patrick B. et al (2006)** investigated that Malondialdehyde levels were higher in thalassaemia compared with SCD., several inflammatory markers appeared higher in SCD. This inflammation in SCD may generate increased levels of γ-tocopherol, leading to decreased tissue peroxidation and injury.

**Rana M.W. Hasanato et al (2006)** reported that that plasma level of the antioxidant vitamins (A, C and E) and serum levels of zinc are significantly lower in patients with sickle cell disease as compared with a control group.

**Vanessa Cumming et al (2006)** concluded that asymptomatic bacteriuria is a significant problem in individual with SCD and may be the source of pathogens in urinary tract infection.

**Debes ray et al (2007)** described that antioxidants vitamin level in heterozygous and homozygous sickle cell disorder in their study. They have
analyse vit C, Vit E and beta carotene in sickle cell anemia and found the level of antioxidant vitamin are low in subjects with sickle cell disorder.

**Katherine et al (2007)** reported that the mounting evidence implicating an imbalance between reactive oxygen and nitrogen species in the pathogenesis of SCD. Further, stated that Decreased anti-oxidant defences in SCD patients and the emerging role of reactive oxygen and nitrogen species in the pathogenesis of SCD provides a platform for the development of novel agents to treat this painful and lethal disease.

**Joanne Thompson et al (2007)** observed that albuminuria and renal function in homogygous sickle cell disease. They further studied that the low level of serum creatinine in sickle cell disease.

**Mariane de Montalembert et al (2007)** concluded that the impaired flow mediated dilation of the brachial artery, probably related to endothelial dysfunction, is observed in children with SCA who lack evidence of arterial stiffness or intimal thickening. They further suggested that therapies intended to increase NO, such as arginine administration should be considered in children with SCA.

**Foluke Fasola et al (2007)** demonstrated that the current evidence of oxidative stress has important roll in the pathophysiology of the deleterious association crisis in sickle cell patients and also reported that total antioxidant effect in the sickle cell patients with view to improve their health.
Sylvie A. Akohoue et al (2007) suggested that Low-grade inflammation and increased oxidative stress are present in adolescents with HbSS in the absence of acute crisis, and their markers are correlated with elevated resting energy expenditure (REE).

Vanusa Manfredini et al (2008) in their study determined oxidative stress has an important role to play in the pathophysiology of sickle cell disease. Sickle cell anemia patients in steady state show oxidative damage in spite of increased defence and suggested that the use of agent that increase the antioxidant capacity of these patients with a view to improving their clinical status.

Petra Niklowitz et al (2008) concluded that the oral administration of CoQ10 in sufficient doses leads to the incorporation of CoQ10 into platelets and white blood cells. Thus, blood cells may provide suitable targets for assessing intracellular CoQ10 concentrations. Intracellular enrichment may support cellular antioxidative defense mechanisms.

Richard Rokyta et al (2008) assessed biochemical marker like C reactive protein, total protein, albumin, total cholesterol, HDL and LDL cholesterol, glucose, triglycerides, reduced glutathione, malondialdehyde (MDA), and total antioxidative capacity in patients with pain in vascular region. They described biochemical changes in blood plasma components might play an important role in pain assessment and pain management.
Enika Nagababua et al (2008) examined that fluorescence arising from heme degradation increases in RBCs with unstable HbS. They further suggested that degradation of the heme moiety in intact hemoglobin and/or degradation of free heme by peroxides are higher in pathological RBCs.

Joy Okpuzor et al (2008) suggested the intervention of medicinal plant in management of sickle cell disease by traditional healer and underlying principal of their usage. They also mentioned the sickle cell erythrocytes are fragile and dehydrated and it is important that minerals and antioxidants are constantly supplied to maintain hydration and membrane integrity.

O. G. Arinola et al (2008) observed that, significantly lower result of total antioxidants and certain trace elements is common in sickle cell disease.

Manfredini V et al (2008) observed that the production of MDA was observed in the serum of sickle cell anemia patients. They also demonstrated that patients with sickle cell are subjected to chronic oxidative stress and are able to oxidative damage in biological macromolecule such as in male and female patients.

Ren H et al (2008) suggested that the lower level of membrane EPA and DHA in blood cell of the HbSS patients, and concluded that due to lipid peroxidation resulting form comprised antioxidants competence.
**Claudia R. Morris et al (2008)** concluded that, decreased glutathione and glutamine levels occur in SCD and may contribute to alterations in the erythrocyte redox environment, leading to compromised erythrocyte integrity.

**Nayma Sultana et al (2009)** studied that increased in osmotic fragility and decreased red cell indices in glucose 6 phosphate dehydrogenase deficiency and vitamin E supplementation help to return these value toward normal.

**Radha Raghupathy et al (2009)** reported that Oral L-glutamine has been shown to significantly increase NAD redox potential and NADH concentration in sickle RBCs, thereby reducing oxidative damage.

**Xiaomei Niu et al (2009)** found that the etiology of pulmonary hypertension in sickle cell disease is multi-factorial, and that pro-inflammatory and angiogenic pathways may interact with the degree of hemolysis in contributing to the development of pulmonary hypertension.

**Suba Krishnan et al (2009)** demonstrated that a strong association between the inflammatory biomarker hs-CRP and hospitalization for Vasso Occlusive Crisis events in paediatric Sickle Cell Disease. and suggested hs-CRP as a potential biomarker for predictive modelling of clinical outcomes in paediatric SCD.
Abhay Bhave et al (2009) noted that every hypochromic microcytic anemia with or without is not always an iron deficiency.

Trine juul et al (2010) summarized ex vivo evidence from mammalian cell culture experiments and in vivo evidence from A. thaliana point to two direct HU targets, RNR and Catalase. Between them, they have the potential to explain many of the pharmacological effects of HU, and the separation of HU effects mediated by these two targets now becomes an important task. they further concluded in their finding the hydroxyurea act as a Catalase activation pro drug. Clinically they have found Catalase activity in circulating cells from untreated chronic myeloid leukaemia.

Nitin John (2010) et al written a review article of clinical profile in sickle cell trait in his article he has mentioned the levels of Superoxide dismutase, Vitamin C, haemoglobin and albumin in sickle cell patients and control. Also given endogenous antioxidants status in patients and control.

Darcielle Bruna Dias Elias et al (2010) showed that during pathogenesis of SCA it is possible to observe an increase in lipid peroxidation. On the other hand, during treatment with HU we did not detect any abnormality in the oxidative parameters, probably due to the short period of treatment of the patients studied.
Abiodun Mathias Emokpae et al (2010) observed that increased level of MDA is accompanied with significantly lower activity level of antioxidant enzymes, and increased acute phase proteins in SCD.

Prakash Hundekar et al (2010) noted that, enhanced oxidative stress in both homozygous and heterozygous SCA patients as compared controls which can increase the severity of disease. They further suggested that oxidant formed by sickle erythrocytes is less likely to be removed effectively with the endogenous mechanism. Therefore, the antioxidant supplementation is required to ameliorate the oxidative stress and improve the clinical course in sickle cell patients.

M. A. Emokpae et al (2010) correlated that increased generation of ROS in SCD patients with renal insufficiency, which is demonstrated by decreased serum activity of antioxidant enzymes. There were also increased markers of inflammation, which correlated significantly with the severity of renal disease. These may increase the mortality and morbidity associated with SCD.

Gizi A et al (2011) concluded that, The findings revealed significant impairment of the glutathione system indicated by reduced GSH (total), GSH (reduced) and GSSG values of SCD patients compared to the control group. ROS expressed as FORT were significantly increased while antioxidant defence expressed as FORD was significantly reduced in SCD group compared to the control group.
Silvia Maria Meira Magalhães et al (2011) stated that Sickle cells spontaneously generate approximately two times more ROS compared to normal red blood cells, this is associated with endothelial dysfunction, inflammation and multiple organ damage and is related to the severity of clinical features.

Thakur et al (2011) suggested that the rationale of using antioxidants in the treatments of SCD. Hence sufficient amount of antioxidant supplementation might be helpful to control oxidative stress of sickle cell anemia patients.

Prakash S. Hundekar et al (2011) observed that increased oxidative stress in terms of elevated serum MDA, serum NO, plasma Protein carbonyl and erythrocytic SOD activity. However, a decrease in the antioxidant capacity of plasma may be due to the overburden of the ROS. The supplementation of antioxidants shows the improved antioxidant capacity of the plasma as well as a decrease in the oxidant levels.

Imoru Momodu (2011) stated that the knowledge of anaemia, leucocytosis, thrombocytosis and reticulocytosis in steady state homozygous sickle cell disease will serve as guide to the clinicians in the management of patients with sickle cell anaemia and most especially in the steady state while tests for the diagnosis of bacterial infections in asymptomatic sickle cell
anaemia should be broadened since leucocytosis may not necessarily be an indication of bacterial infections in this condition.

**Seema tripathi et al (2011)** described that urea, creatinine bilirubin and SGPT concentration in sickle cell anemia. They also noted there is a alteration in protein metabolism as well as total protein and albumin was decreased. they have demonstrated adverse effect of renal function and hepatic function under the stress of sickle cell anemia.

**L.M.S. Vinna – Baracioli et al (2011)** noted that Hb S and iron affect blood cells, and trigger oxidative processes and generation of free radicals with potential for lipid peroxidation. They analyzed the values that indicate antioxidant capacity and total lipid peroxidation, and found that the presence of the allele mutation in the HFE gene contributes to the variation, however, its presence is not sufficient to significantly alter antioxidant capacity or lipid peroxidation. The βs allele proved to be involved at a statistically significant rate when the patient was homozygous for the allele, and with an increase in lipid peroxidation in sickle cell disease patients. Antioxidant capacity was found to be increased in heterozygous Hb S carriers.

**SE Cox et al (2011)** studied that the link between SPO₂ variability and vitamin C deficiency in sickle cell anemia, they have concluded that low vitamin C correction are result SPO₂ variability and hypoxia.
Cergueira BA et al (2011) evaluated that association between serum level of IL-18, uric acid, haemolytic markers, and inflammatory molecule in sickle cell anemia patients. IL-18 and uric acid level were correlated closely with markers of hemolysis, endothelial dysfunction and other cytokine levels. Their finding suggested probable influences of IL-18 and uric acid in the pathophysiology of vascular occlusion in sickle cell anemia.

Kalyan Goswami et al (2011) found in their study probable impact of oxidative stress on erythrocytes membrane lipid and suggested that pathogenic determinant in sickle cell disease. They also found crucial association of oxidative membrane in this haemoglobinopathies.

Tanveer jilan et al (2011) reported that vitamin E has multiple non-antioxidant functions along with its well-established basic cellular antioxidant function. Vitamin E has the potential to be affectively used for preventing/and or treating some types of the human anemia due to its putative role in promoting erythropoiesis, enhancing the integrity and stability of erythrocyte membrane proteins and lipids, and reducing the oxidative stress-induced erythrocyte fragility and lysis. This results in increasing RBC survival and improves blood haemoglobin levels.

Ezeiruaku et al (2011) worked on activity level of some erythrocyte enzyme like glutathione S transferase, NADH ferricyanide reductase and serum LDH in three human genotype like HbSS, HbAS, and HbAA. The
comparative study showed the intermediate values in the activities of the enzymes obtained from the serum of HbAS subjects, which should be a reflection of the heterozygous nature of the haemoglobin and the associated haemolysis of the blood erythrocytes. Because many conditions contributed to the increased activities of these enzymes and their elevated values were assumed in some quarters to be non-specific findings. This is disproved in this study, because of the comparative nature of the studies that did not show elevated values in normal HbAA subjects.

Erfan Nur et al (2011) noted that SCD is characterized by increased generation of ROS resulting in oxidative damage of various cell types including erythrocytes and the endothelium. The chronically elevated oxidative stress in SCD might play a significant role in the development of SCD related organ complications. Secondary products of oxidative stress may potentially serve as biomarkers of disease severity in SCD. The potential of antioxidants and agents with antioxidative effects for preventing or delaying the development of organ complications in sickle cell patients deserves thorough investigation.

Sanjeev shyam Rao (2012) conclude that moderate to severe anemia, low MCV and high HbF dominate the hematological profile of South Gujarat SCD children.
Edis belini et al (2012) reported that, oxidative stress and antioxidant capacity in sickle cell anemia patients receiving different treatment and medication for different period of time. They have studied the effect of drug detersirox and hydroxyurea as well as folic acid in these patients.

Chirico et al (2012) observed that decreased activity of Catalase in sickle cell anemia patients.

Shuchismita Behera et al (2012) concluded that homozygous SCA cases found to have significantly lower levels of vitamin A antioxidant as compared to heterozygous or control groups

Arlet JB et al (2012) suggested that the kidney function deterioted by analysing serum uric acid level is one of the early markers for renal dysfunction in sickle cell patients.

M. A. Emokpae et al (2012) concluded that the increase oxidative stress and high atherogenic index in CKD may accelerate the process of cardiovascular complications in adult SCD patients.

E Stephan et al (2013) reported reduced level of both total glutathione and GSH/GSSG ration in Sickle cell disease.

Bastawy et al (2013) stated that Glutathione Peroxidase level in the body are in close relation with the glutathione which is the most important antioxidant present in cytoplasm of the cell.
Wali U et al (2013) reported decrease level of antioxidant vitamin E, C & A in sickle cell anemia patients.

Wiesten et al (2014) suggested that erythrocyte Glutathione reductase is key enzyme in RBC metabolism. It is a flavanoids protein and its activity relies on sufficient flavin intake. Alleged GR deficiency are usually due to shortage of this cofactor and are easily corrected by supplementation of riboflavin in food.

Wali U et al (2014) observed decrease level of antioxidant vitamin E, A & C in both homozygous and heterozygous group as compared to control subjects.