academicJournals

Vol. 7(48), pp. 3452-3476, 25 December, 2013
DOI: 10.5897/JMPR2013.5333x
ISSN 1996-0875 ©2013 Academic Journals
http://www.academicjournals.org/JMPR

Journal of Medicinal Plants Research

Full Length Research Paper

Chemical constituents and biological activity of medicinal plants used for the management of sickle cell disease - A review

Kunle Oluyemisi Folashade and Egharevba Henry Omoregie*

Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development, Idu-Industrial Area, Abuja, Nigeria.

Accepted 12 November, 2013

Since 1910 when sickle cell disease was first reported by Dr. James Herrick and the subsequent characterization by Linus Pauling who hypothesized on the nature of sickle cell haemoglobin (HbS) and its role in sickle cell anemia in 1952, the cure and treatment for the disease has remained a challenge for the entire humanity, with millions of sufferers around the world, and the attendant negative social economic impact. With a current sickle cell trait (healthy carriers who have inherited the mutant gene from only one parent) prevalence of between 10 to 40% across equatorial Africa, 1 to 2% on the North African coast and < 1% in South Africa, current orthodox treatment regimens continue to give unsatisfactory outcome. The use of herbal remedies especially in the developing or low income countries has made treatment more affordable and accessible, and thus, appears to be yielding some positive prospect in drug development, especially with the development of NIPRISAN™ in 1997 by the National Institute for Pharmaceutical Research and Development (NIPRD) in Nigeria. Most of these herbal remedies exploit the combined pharmacological activities of medicinal and aromatic plants widely available in the tropics. Such pharmacologic activities include antioxidant, anti-inflammation, antipyretic, antidehydration, ion-chelating, etc. This review exposed the knowledge-gaps in the chemical constituents of these plants and suggests areas of further research and development focus.

Key words: Sickle cell disease, medicinal plants, chemical constituents, antioxidants, phenolics.

INTRODUCTION

Sickle cell disease (SCD) or sickle cell anaemia (SCA) is a genetic disorder usually associated with persistent ulcers, enlanged spleen, painful swellings of the digits and joints, shortness of breath, heart palpitations, abdominal pains, muscular aches, pains, anemia and sometimes death (Afolabi et al., 2012; Sofowora, 2008). The disease is caused by a single base mutation of adenine to thymine, which results in a substitution of valine for glutamic acid at the sixth codon of the β-globin chain (βS) (Koch et al., 2002). The substitution in βS of polar glutamic acid residue with a non-polar valine molecule generates a sticky patch on the β-globin chain (Martin, 1983). The sticky patch results from the ability of the hydrophobic valine side-chain to readily fit into a hydrophobic pocket formed from a β88 leucine residue and a β85 phenylalanine residue on an adjacent molecule. This substitution has a profound structural and pharmacological consequence on the resulting

*Corresponding author. E-mail: omoregieegharevba@yahoo.com. Tel: +234-808-582-6500.

haemoglobin (HbS).

In conditions of reduced oxygen tension, HbS molecules undergo nucleation, growth and subsequent alignment of the molecule into microfibrils parallel to each other with the resultant membrane deformity and damage. Thus, the haemoglobin from sickle cell form relatively insoluble polymer under hypoxia condition, creating a crescent-shaped erythrocytes cell which may give rise to micro-vascular occlusion leading to serious fatal crises. The polymerization and occlusion are particularly aided in situation of increased dehydration during crisis (Afolabi et al., 2012; Mehanna, 2001). Initially, the observed sickling is reversible upon reoxygenation of the system. But repeated oxygenation and deoxygenation cycle lead to irreversible sickled cell (Sofowora, 2008). The cell undergoing sickling loses K^+ and gains Na^+ ions without any significant change in total cation level. Sickled cells have also been reported to be low in Zn^{2+} and increased Ca^{2+} level also occur in irreversibly damaged sickled cell (Brewer and Oelshelegel, 1974; Jasen et al., 1973).

The polimerised HbS stretches the cell membrane interferening with the Ca^{2+}-activated, Mg^{2+}-dependent ATPase (Ca^{2+} pump) responsible for maintaining membrane integrity. Declining Ca^{2+} pump efficiency may lead to premature ageing and formation of rigid sickled cell. The increased level of ATP required to maintain cellular integrity leads to the accumulation of 2,3-diphosphoglycerate (DPG), which binds to haemoglobin, facilitating rapid release of oxygen from the blood cell and partial hypoxia condition in the cell. The low oxygen tension and subsequent absorption of carbon dioxide creates local acidosis, early sickling, high blood viscosity, increased adhesion of deformed cells, slower blood flow and *in vivo* clotting. The phenomena lead to haemolysis and microvascular occlusion, tissue/organ infarction and painful crises (Sofowora, 2008). These clinical features of the sickle cell disease do not appear until after the first six months of life, at which time most of the foetal haemoglobin (HbF) has been replaced by HbS, which is the basis for the use of foetal haemoglobin inducers in orthodox therapy.

The sickle cell gene (βS) occurs widely throughout Africa, part of Asia, the Arabian Peninsula and part of Southern Europe. Nigeria, Ghana, Gabon and Zaire have been identified as countries with high prevalence of the sickle cell gene in Africa, with a carrier rate of about 10 to 40% of the population and accounting for approximately 80,000 infant deaths per year (Uzoegwu and Onwurah, 2003; Wainscoat, 1987). Sickle cell disease occurs with a much lower incidence in parts of Italy, Greece, the Middle East and India. It has been suggested by some workers that the βS mutation may have arisen independently in Africa and Asia and the frequency fuelled by malaria (Weatheral et al., 1983).

Current orthodox approach to management of SCD

Despite the good understanding of the molecular nature of the disease, a cure for sickle cell anemia is still unavailable. Various approaches have been adapted in an effort to find agents that inhibit the polymerization of haemoglobin and hence prevent or reduce the occurrence of crises in sickle cell disease (Iyamu et al., 2002; Akojie and Fung, 1992). In this regard, oxygen, carbon monoxide and sodium nitrite were used to reduce the amount of deoxyhaemoglobin. Focus has also been on developing antisickling agents which act by blocking or inhibiting activities in the HbS leading to polymerization (Chikezie et al., 2011). Treatment strategies for sickle cell anemia since the early times of discovery in 1910 have focused mainly on prophylactic measures to alleviate the painful crises through administration of analgesics, antipyretics, intravenous fluids or hydrants or antidehydrants, oral antibiotics such as penicillin and the anticancer drug hydroxyurea as foetal haemoglobin inducer.

Butyrates and decitabine have also been tried for foetal haemoglobin induction (Sauntharajah et al., 2008; Stocker et al., 2003; McGoron et al., 2000). Fetal hemoglobin is believed to interfere with the polymerized globin chains and also inhibits polymerization of the HbS. Lactate dehydrogenase (LDH) inhibitors such as hydroxyurea, erythropoietin and tucaresol preparation have been found to be effective in SCD crises management (Okpuzor et al., 2008). Hydroxyurea has been approved by the United States Food and Drug Administration as anti-sickling agent/drug for the management of the disease (Mehanna, 2001). Further attempts at finding cure led to successes in bone-marrow transplant or hematopoietic cell transplantation (HCT). However, this has proven to be too expensive with poor success rate. Other attempts have been focused on finding new anti-sickling agents that specifically bind to HbS, which led to the development of some anti-sickling agents such as 5-hydroxymethyl-2-furfural (5HMF) (Abdulmalik et al., 2005), certain amino acids such as phenylalanine, lysine and arginine (Anosike et al., 1991), 2-imidazolines such as clotrimazole (Chang et al., 1983), and other Gardos channel inhibitors like senicapoc [bis(4-fluorophenyl)phenyl acetamide], dimethyl adipate, vaso-active molecules like endothelins were also developed (Nagalla and Ballas, 2010) (Figure 1).

Gardos channel inhibitors like clotrimazole, magnesium and ICA-17043 act by preventing dehydration (Okpuzor et al., 2008). Deoxygenation increases membrane permeability to Mg^{2+} resulting in a net loss of intracellular Mg^{2+}. The modulation of the activities of the three membrane-based ATPases (Na^+, K^+ and Ca^{2+}) have been shown to be significantly lowered in sickle cell patient (HbSS) erythrocytes, while Mg^{2+} ATPases was

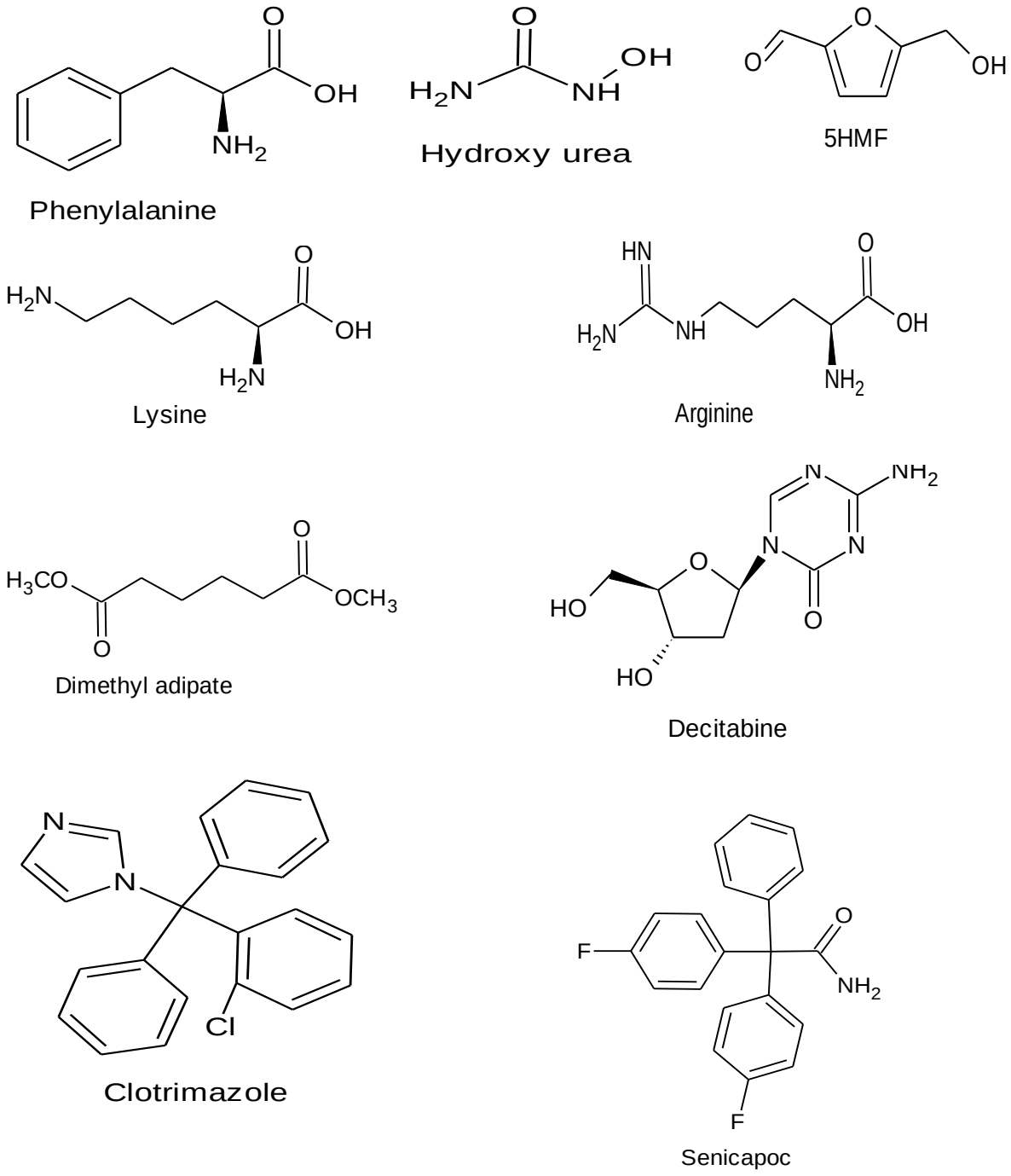


Figure 1. Compounds used or showing great potential for use in the management of SCD.

significantly higher in HbSS than for normal patient (HbAA) erythrocytes. Ca^{2+} has also been found to play a significant role in low K^{+} and Na^{+} permeability of erythrocyte membrane, which helps to maintain the normal rate of cation leakage from the cell. Indeed it had been suggested that sickling of red cells could be reversed if excess Ca^{2+} in the red cells is pumped out (Okpuzor et al., 2008). There are also reports on the capability of some anti-malarial drugs and oral iron chelators to distort/alter certain red blood cell elements/physicochemical properties, which may be helpful in the management of the disease (Chikezie et al.,

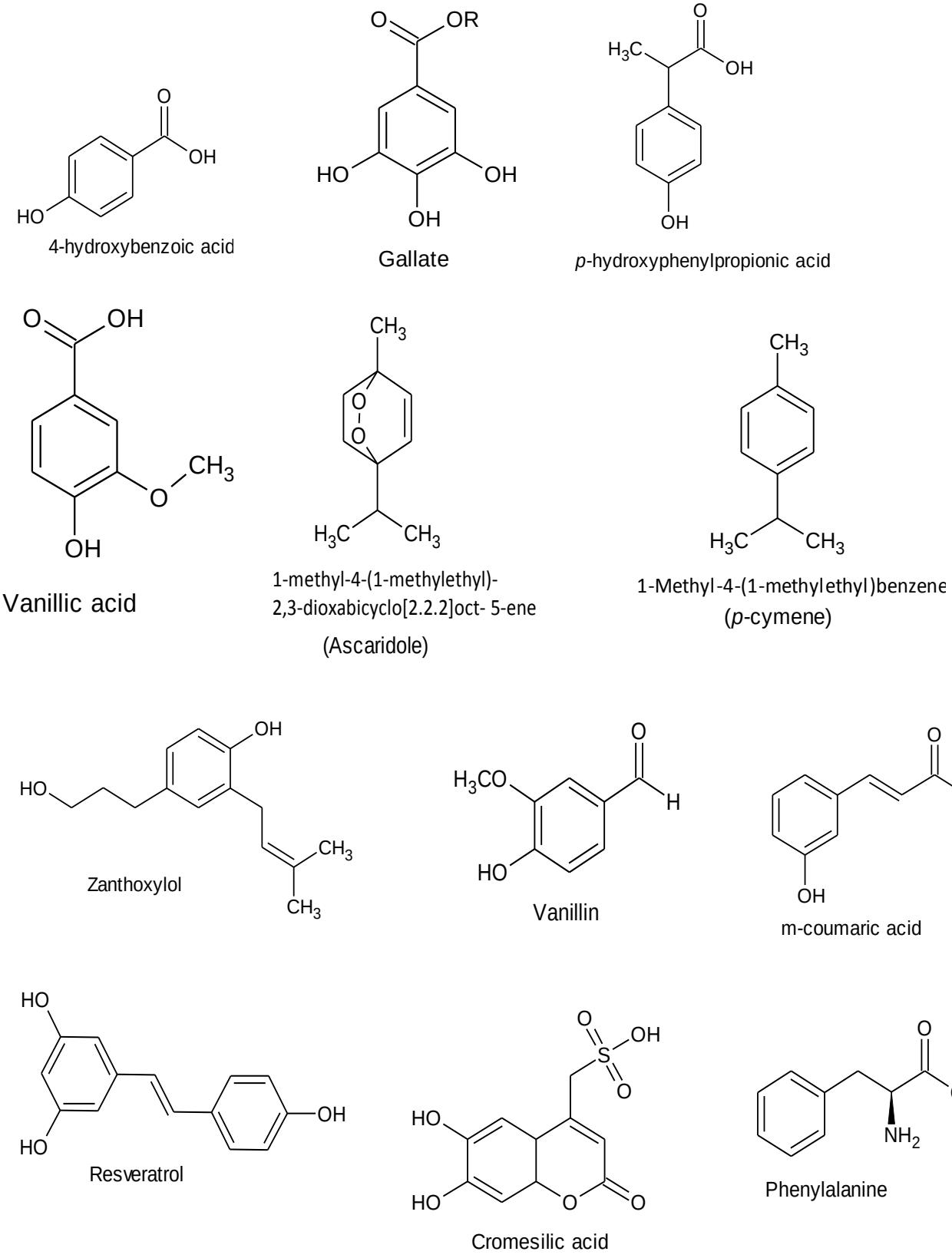
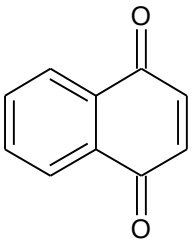
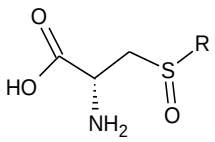


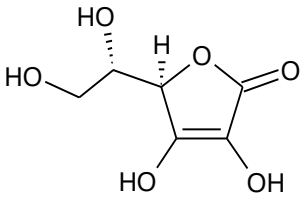
Figure 2. Structures of active phytochemical components of medicinal plants used in SCD.



2-hydroxy-1,4-napthoquinone
(Lawsone or Hennatannic acic

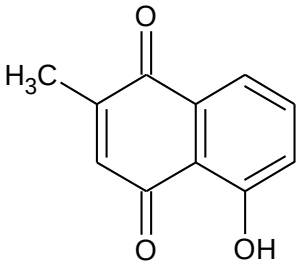


L-Cysteine Sulfoxide



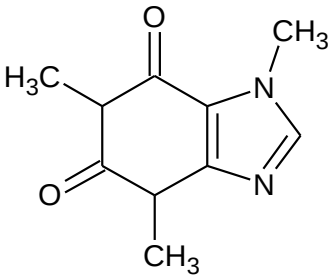
(5*R*)-[(1*S*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one

(Ascorbic acid or Vitamin C)



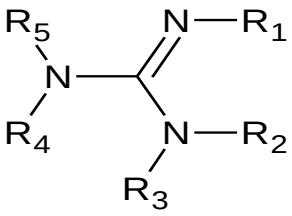
5-hydroxy-2-methyl-naphthalene-1,4-dione

(Plumbagin)

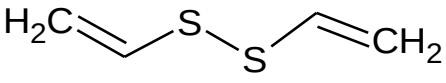


1,3,7-Trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

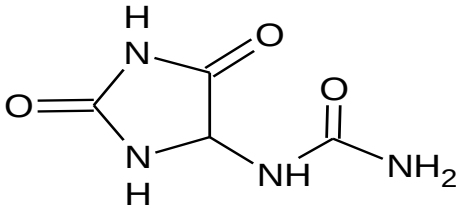
(Caffeine)



Guanidine alkaloid

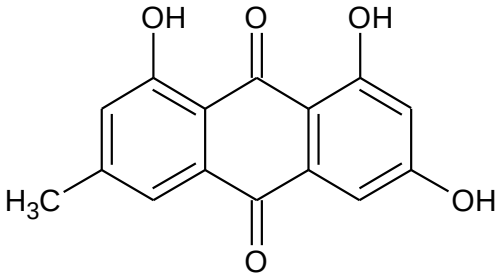


Diallyl disulfide



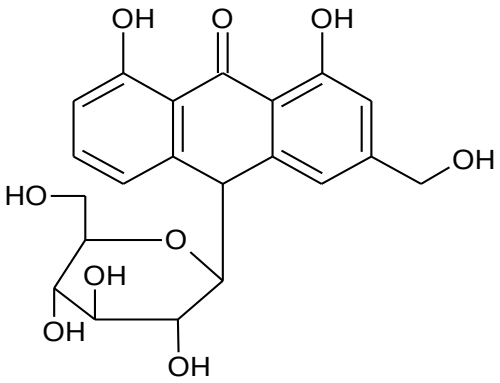
(2,5-Dioxo-4-imidazolidinyl) ure

(Allantoin)



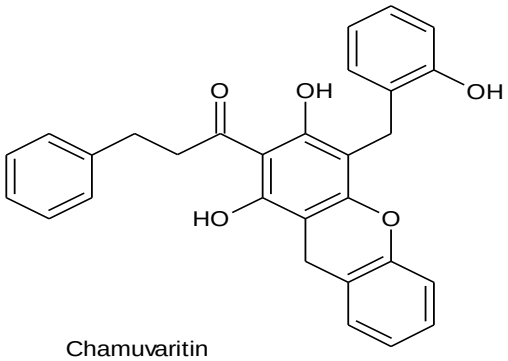
6-methyl-1,3,8-trihydroxyanthraquinon

(Emodin)

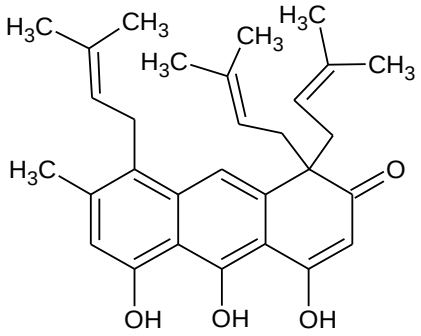


(Aloin A)

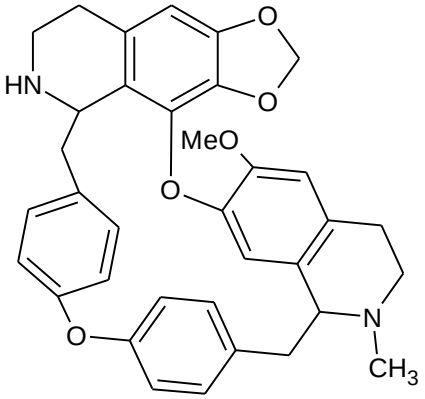
Figure 2. Contd.



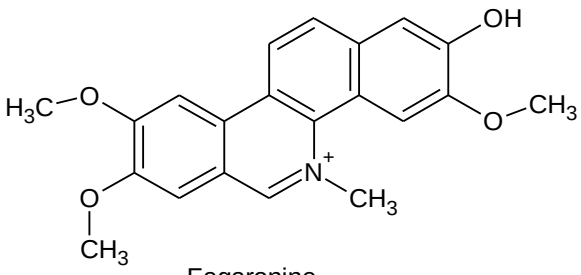
Chamuvaritin



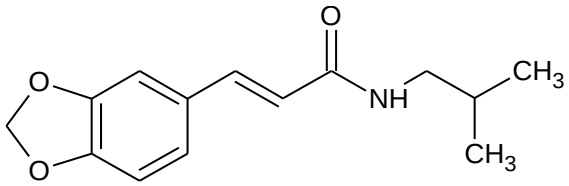
Harunganin



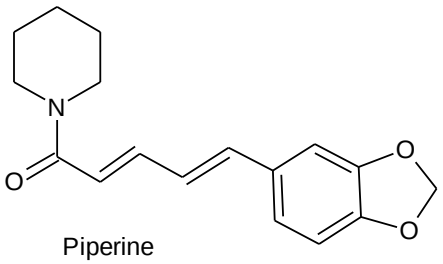
Cepharantine



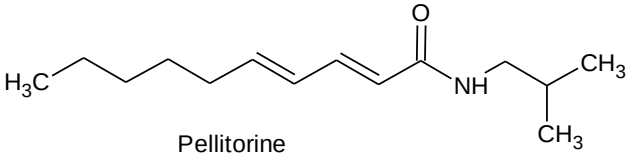
Fagaronine



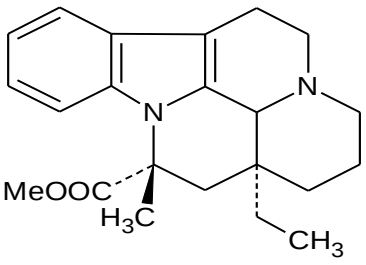
Fagaramide



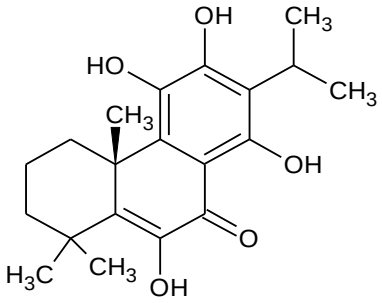
Piperine



Pellitorine

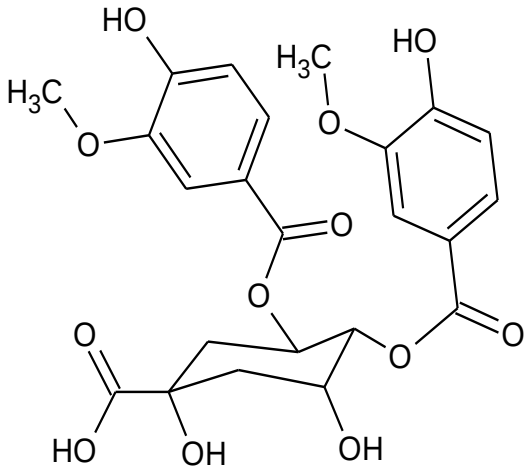


Vincamine

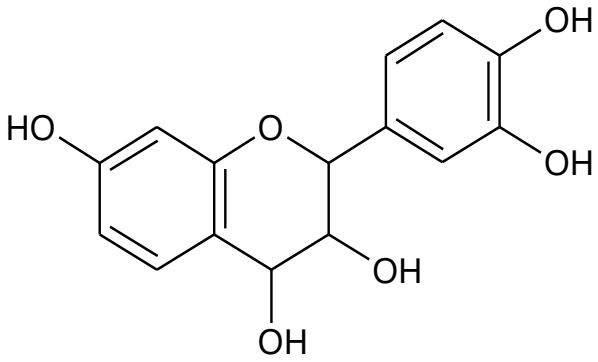


(Coleon U)

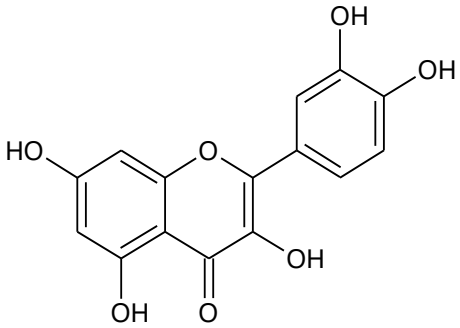
Figure 2. Contd.



4,5-O-divanilloylquinic acid

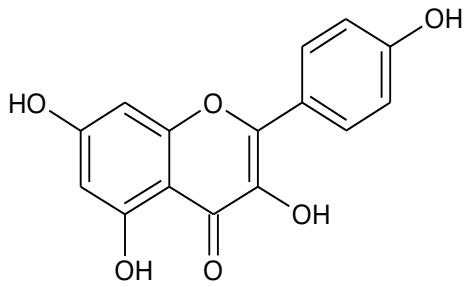


3',4',7-trihydroxyflavan-3,4-diol



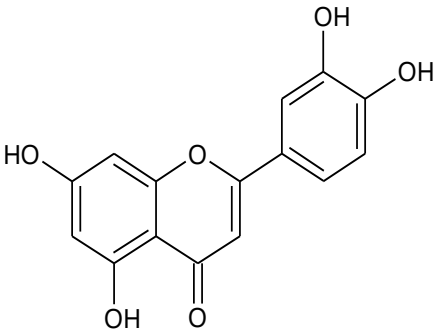
2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy
-4*H*-chromen-4-one

(Quercetin)



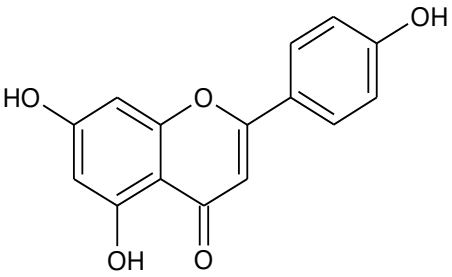
3,5,7-trihydroxy-2-(4-hydroxyphenyl)-
4 *H*-1-benzopyran-4-one

(Kaemferol)



2-(3,4-Dihydroxyphenyl)-
5,7-dihydroxy-4-chromenone

(Luteolin)



5,7-Dihydroxy-2-(4-hydroxyphenyl)-4*H*
-1-benzopyran-4-one

(Apigenin)

Figure 2. Contd.

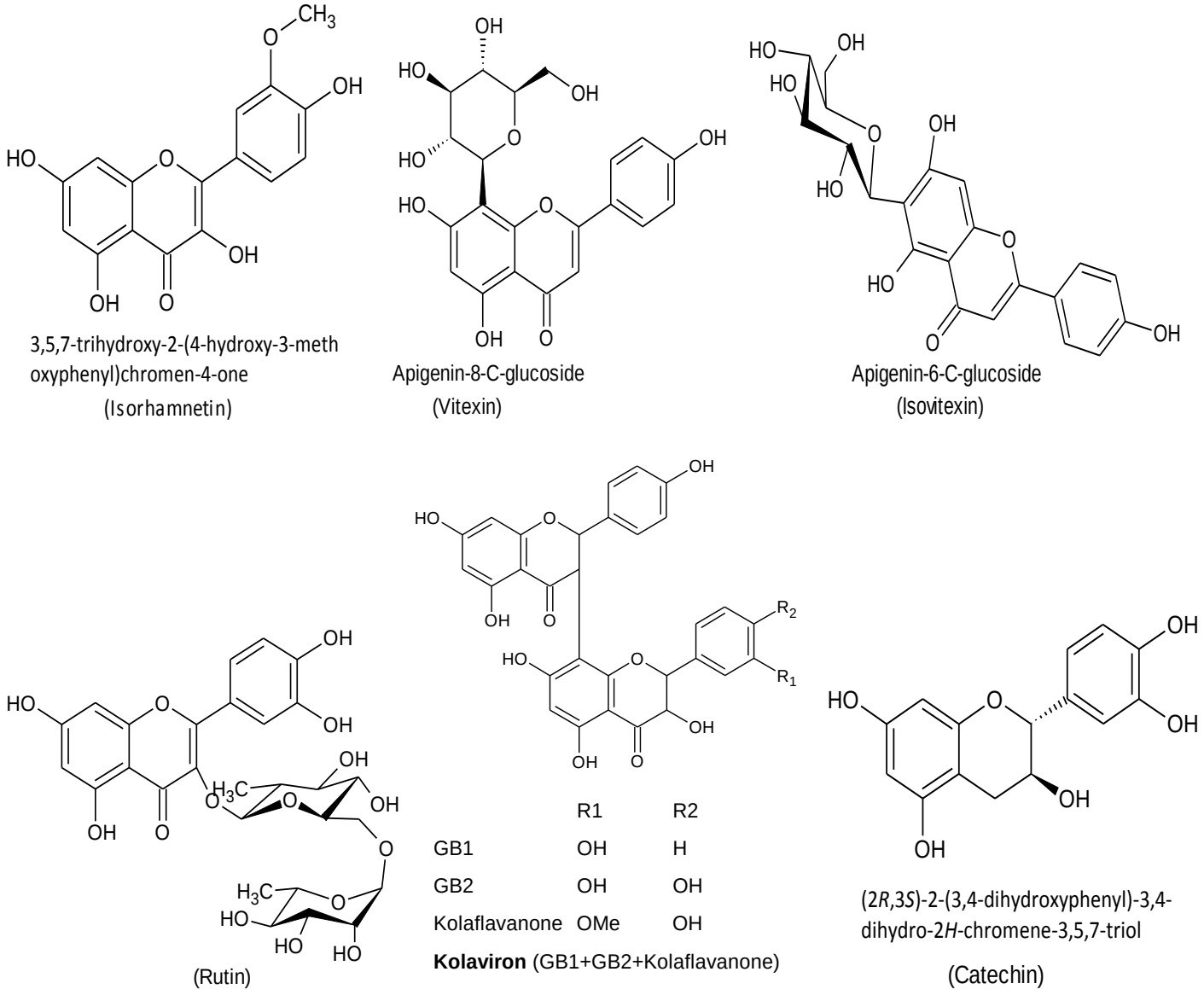
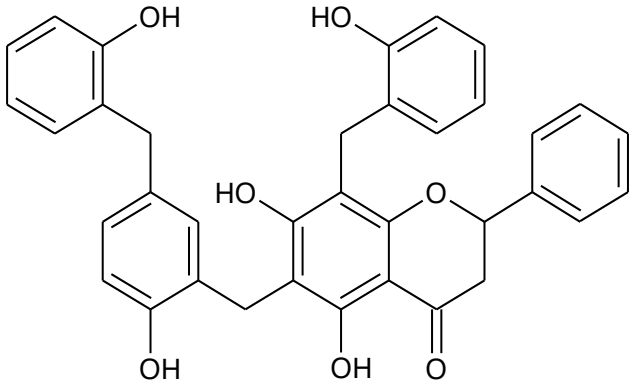


Figure 2. Contd.

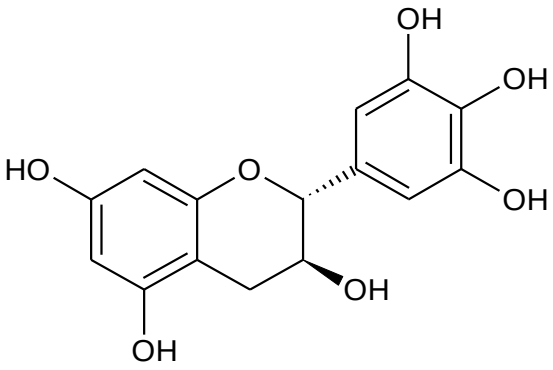
2011, 2010, 2009a, b; Chikezie, 2009, 2008; Gibson et al., 1998). However, these approaches are yet to give the much desired beneficial effects, hence there is the need for more research in the field (Iyamu et al., 2002).

The use of herbs for the treatment of patients with (SCD) is a common practice especially in the rural communities of West Africa where SCD is endemic. Current indigenous drug development processes also use active crude extracts (ACEs) from medicinal plants from proven traditional recipes in their formulations. An example is NIPRISAN^{TM}, a herbal drug developed by the National Institute for Pharmaceutical Research and Development (NIPRD), and widely in use in Nigeria, India and the United States of America, which has shown great indication for success (Ameh et al., 2012; Wambebe et al., 2001). This may have been possible due to synergistic effect of the chemical components of the constituent herbs. Hence, the observed therapeutic effect of this phytomedicine may be as a result of combined antisickling, antipolymerization, antidehydration and antioxidants effects from the component plants, which is typical of most herbal remedies.

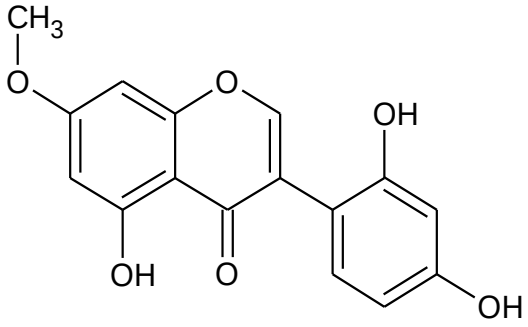
Several authors and researchers have reported a number of herbal recipes and formulations from medicinal



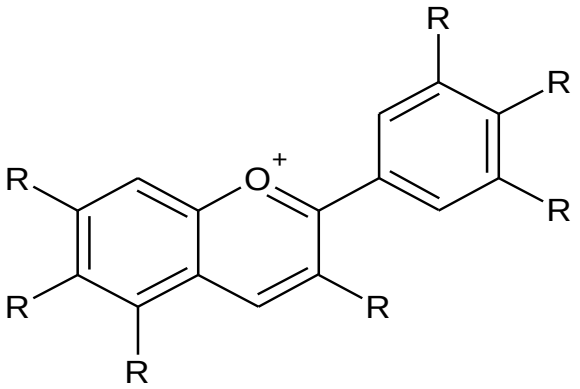
(Uvarinol)



(Epigallocatechin or (+)-gallocatechin)

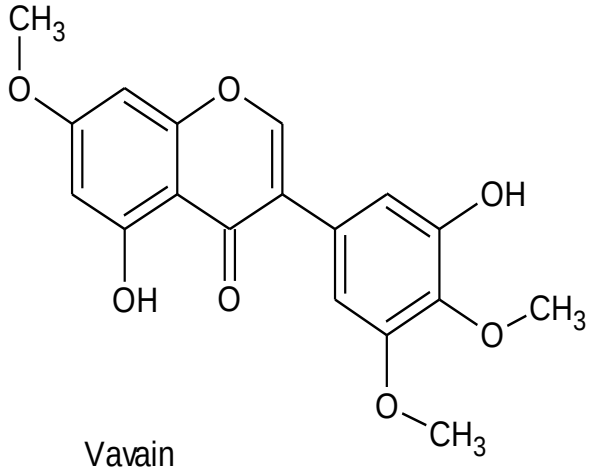


5,2',4'-Trihydroxy-7-methoxyisoflavone,
(Cajanin)

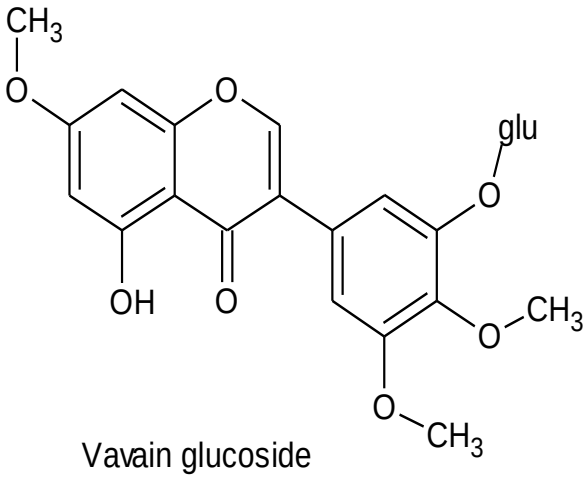


R = Hydrogen, hydroxyl or alkoxyl gr

(Anthocyanidins)

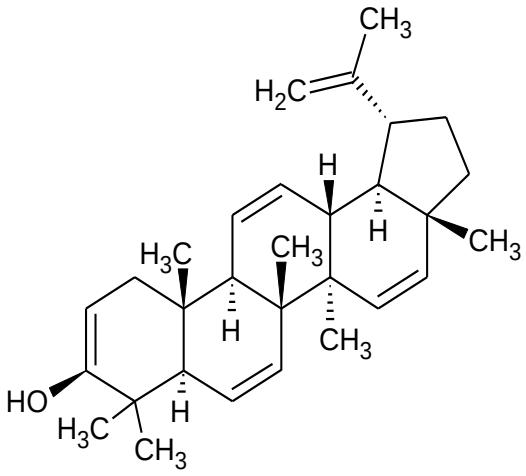


Vavain

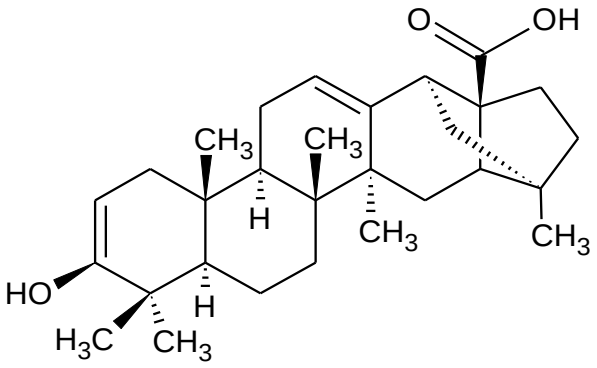


Vavain glucoside

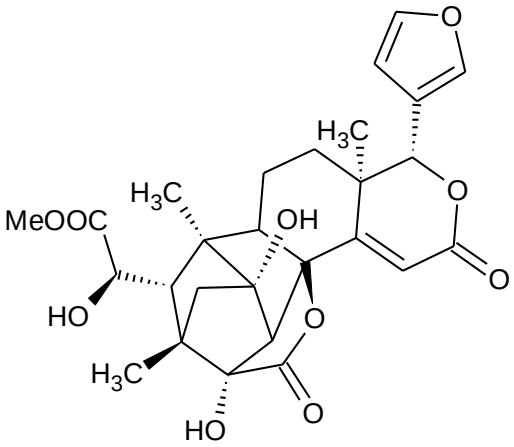
Figure 2. Contd.



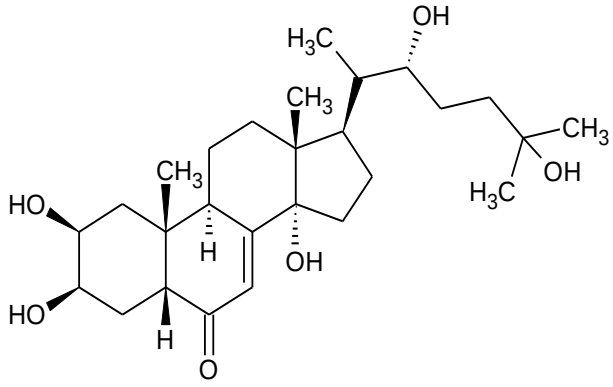
Lupeol (Fagarasterol)



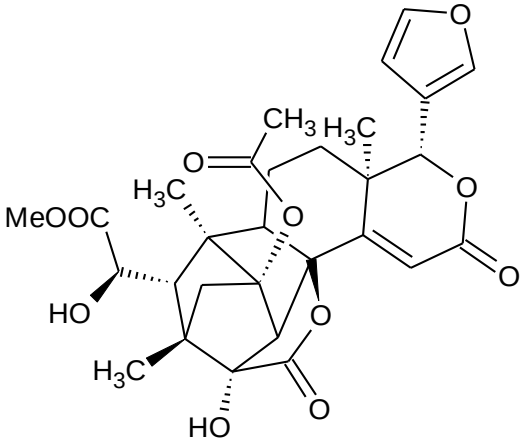
Pfaffic acid



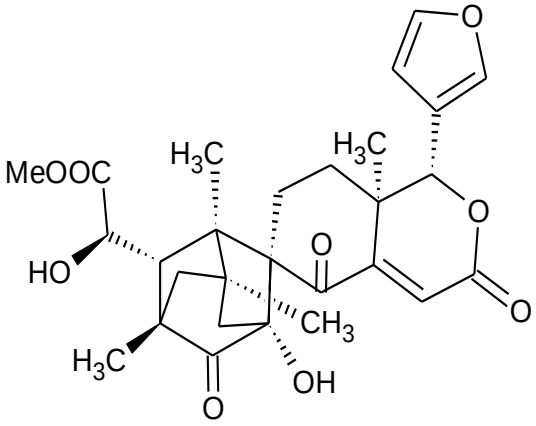
Senegalensions A



Ecdysone

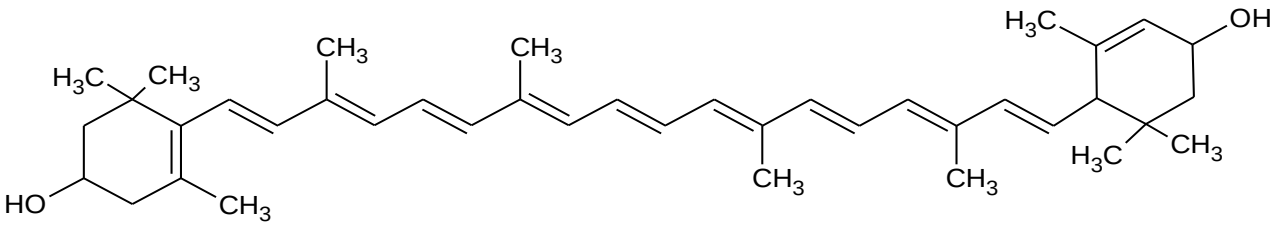


Senegalensions B

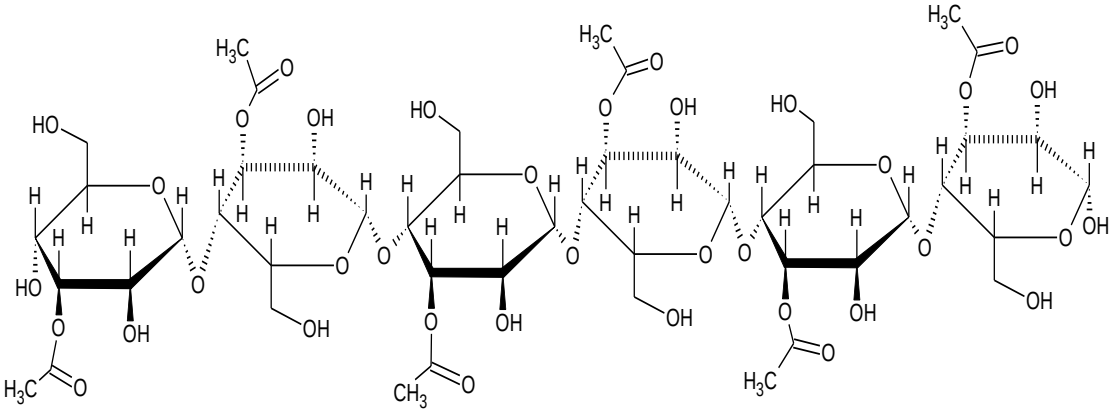


Senegalensions C

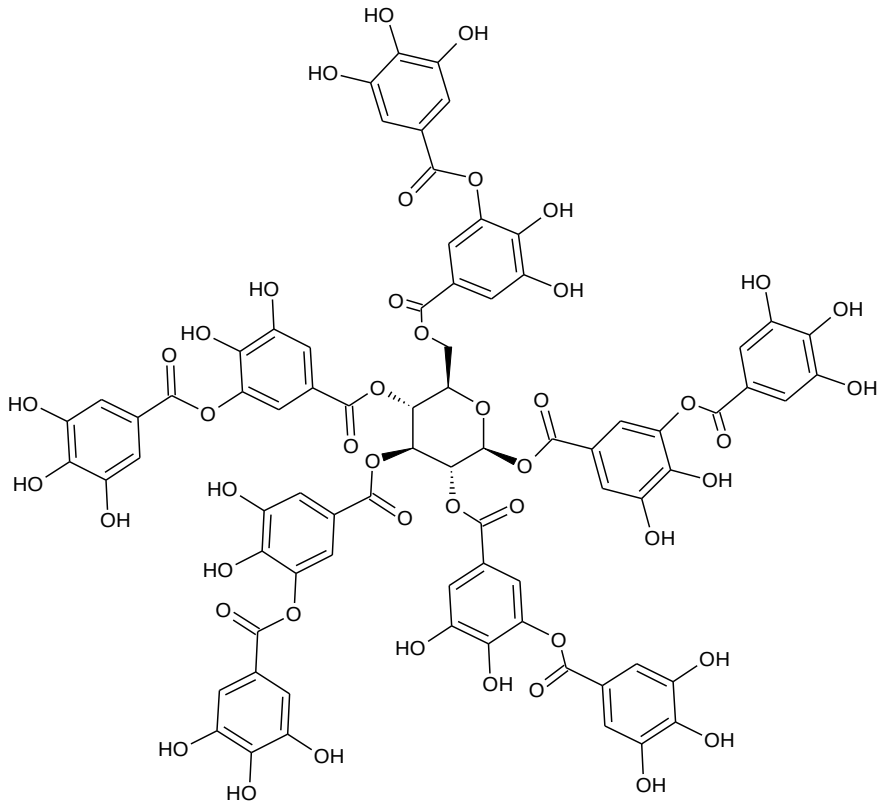
Figure 2. Contd.



Lutein (a Carotenoid)



Acemanna



(Tannic or gallotannic acid)

Figure 2. Contd.

plants for the management of SCD. These medicinal plants have been shown to have shown different activities in SCD condition, ranging from anti-sickling, anti-aggregating, anti-polymerization, radical scavenging or antioxidant, anti-inflammatory, analgesic, anti-pyretic, anti-dehydrating to anti-osmotic effect, etc. All these effects add up to give more stable and tolerable patient condition (Sulaiman and Gopalakrishnan, 2013; Afolabi et al., 2012; Ameh et al., 2012; Chikezie et al., 2011; Nagalla and Ballas, 2010; Dong et al., 1998). It is against this backdrop that this review has become very necessary to periscope medicinal plants used in the management of the disease, their reported pharmacological activities and the active constituents or major chemical compounds found in the plants. This may provide a reservoir of knowledge and understanding of some of the active recipes that have been formulated by workers in the field. The review also attempts to open up new thought direction in the deployment of combination therapy for active crude extracts in the management of the disease.

Medicinal plants used in the management of sickle cell disease

Considering all genetic disorders to which man is known to be liable, there is probably no other that presents such a vista of problems and challenges quite comparable to SCD-related disorders. Due to the debilitating effect and cost of managing the SCD, research has been on-going to determine the efficacy of the use of medicinal plants to tackle the multiple challenges presented in the disease. In the USA with about 80,000 sufferers, the disease was associated with a cost of about $475 million in 2003 (Obodozie et al., 2009). The issues of availability, affordability, perceived safety and efficacy of herbal drugs have continued to fuel the growing use of herbals in-lieu of orthodox drugs. In addition, research interest in medicinal plant as a potential source of new and reliable antisickling agent is also on the rise due to the fact that plants have been established as a reservoir of leads/hits chemical compounds in the drug discovery research. Some of these plants have antioxidant, anti-inflammatory, antimicrobial and anti-adhesion properties while others may be involved in boosting the immune system, working as analgesic, aphrodisiac or aiding general metabolism for wellbeing. The cocktail encompassing all these properties have remained very desirable to the users of herbal medicines.

The knowledge of traditional herbal practice has played a positive role in the use of medicinal plants in the management of sickle cell disease with a great degree of success over time. This traditional knowledge has played significant role in reducing the time frame for lead identification in the preclinical study process. Hence much information has flooded the public domain on the active constituents and possible mode of action of these plants, which has become a great scientific and economic resource.

Reports and information from various ethnomedical practices normally use recipes with more than one plant or plant parts. Sometimes plants from the same family are used in a recipe while recipes may contain plants from different families. Some recipes also include non-plant and animal materials, for example, potash (Wambebe et al., 2001). Such solid mineral components are usually used to provide electrolyte buffer and balance pH, which may be necessary for absorption and bioavailability of the active principles.

Plants reportedly used in SCD ethnomedicine, some of which have been scientifically proven, belong to the following forty-four families; Fabaceae, Bombacaceae, Zingiberaceae, Euphorbiaceae, Alliaceae, Liliaceae, Annonaceae, Theaceae, Caricaceae, Malvaceae, Chenopodiacea, Vitaceae, Rutaceae, Poaceae, Cyperaceae, Burseraceae, Meliaceae, Myrtaceae, Clusiaceae, Hyperricaceae, Flacourtiaceae, Cannabaceae, Anacardiaceae, Geraniaceae, Convolvulaceae, Acanthacea, Lythraceae, Asclepiadaceae, Rubiaceae, Lauraceae, Phytolaccaceae, Amaranthaceae, Piperaceae, Plumbaginaceae, Papilionaceae, Palmaceae, Lamiaceae, Poaceae, Menispermaceae, Combretaceae, Dilleniaceae, Ulmaceae, Asteraceae and Sterculiaceae (Table 1).

About seventy-one (71) plants belonging to the named families are documented in this review. Some of these plants have been reported with a wide array of biological activities including, antiviral, antifungal, antimalarial, antimicrobial, antidiabetic, anticancer, anti-inflammatory, anti-tumor, antiulcer, immunomodulatory and antioxidant activities. For example *Zanthoxylum zanthoxyloides* (Lam.) Waterm, has a wide range of biological activities but found to be very potent for the management of SCD. However, the pharmacological activities of some of these plants are more specific than general in disease situations. Plants with proven antioxidant activities are very prominent among the plants documented in this review. The active chemical components (Figure 2) in these plants are as varied as the species. However, there are many instances where the plants share same active components and hence may have exact same pharmacological effect. From Table 1, it is evident that phenolics or polyphenolics are major components of most of the plants used in SCD. Other active chemical components found in some of them include benzoic acid derivatives, quinidine derivatives, aromatic amino acids and their derivatives, amides, quinone derivatives, limonoids, urea derivatives and furan derivatives.

Table 1. Chemical constituents and biological activity of medicinal plants used in the management of SCD.

S/N	Medicinal plants	Part(s) used	Biological action	SCD action	Major chemical components	Main active constituent(s) plant	Reference
1	*Acacia catechu* Willd (Fabaceae)	Leaf	Hypoglycemic, anti-inflammatory, anti-bacterial, anti-platelet aggregatory, anti-hypertensive, analgesic, anti-cancer, and antiatherosclerotic	Anti-platelet aggregatory, antioxidant and free radical scavenging	Phenolic acids; alkaloids; terpenes; tannins; flavonoids; 4-hydroxybenzoic acid; kampferol; quercetin; catechin; epicatechin; afzelechin; epiafzelechin; mesquitol; ophioglonin; aromadendrin; phenol.	4-hydroxybenzoic acid; kampferol; quercetin	Sulaiman and Gopalakrishnan (2013), Li et al. (2010)
2	*Acacia leucophloea* Roxb. (Fabaceae)	Leaf	Hypoglycemic, anti-inflammatory, anti-bacterial, anti-platelet aggregatory, anti-hypertensive, analgesic, anti-cancer, and antiatherosclerotic	Anti-platelet aggregatory, antioxidant and free radical scavenging	Phenolic acids; alkaloids; terpenes; tannins; flavonoids; n-Hexacosanol; β-Amyrin; β-Sitosterol	-	Sulaiman and Gopalakrishnan (2013), Gupta et al. (2010)
3	*Acacia nilotica* (L.) Willd. ex Del. (Fabaceae)	Leaf	Hypoglycemic, anti-inflammatory, anti-bacterial, anti-platelet aggregatory, anti-hypertensive, analgesic, anti-cancer, and antiatherosclerotic	Anti-platelet aggregatory, antioxidant and free radical scavenging activities.	Phenolic acids; alkaloids; terpenes; tannins; flavonoids; cyanogenic glycosides; Phlobetannin; cyclitols; fatty acids; seed oils, fluoroacetate; gums; nonprotein amino acids; m-digallic acid; gallic acid; protocatechuic acid; ellagic acids; leucocyanidin; (-) epicatechol; apigenin 6-8-bis-D-glucoside; rutin; pyrocatechol; (+) – catechin; (-) epigallocatechin-5,7-digallate	Tannin; catechin; 3,4,7- trihydroxy flavan-3,4-diol	Sulaiman and Gopalakrishnan (2013), Malviya et al. (2011)
4	*Acacia xanthoploea* Benth. (Fabaceae)	Stem bark	Antimalarial, antisickling	Antisickling	Anthocyanins; carotenoid; coumarins	-	Sofowora (2008)
5	*Adansonia digitata* L. (Bombacaceae)	Bark, fruit, leaf	Antioxidant, antiviral, antimicrobial.	Antisickling, boost red blood and white blood cell count	Vitamins C and E.	-	Sahu et al. (2012), Mpiana et al. (2007), Adesanya et al. (1988)
6	*Aframomum alboviolaceum* (Ridl.) K. Schum. (Zingiberaceae)	Rhizome, leaf	Antimicrobial	Antisickling	(E)-labda-8(17),12-diene-15,16-dial; (E)-β-17-epoxy-labd-12-ene-15,16-dial; methyl (E)-14,15-epoxylabd-8(17),12-dien-16-oate.	-	Sahu et al. (2012), Mpiana et al. (2007), Abreu and Noronha (1997), Marlier et al. (1993)
7	*Alchornea cordifolia* (Schum. & Thonn.) Muell. Arg. (Euphorbiaceae)	Leaf	Anti-inflammatory, antibacterial	Anti-anaemia, anti-sickling	diisopentenyl guanidine; triisopentenyl guanidine; β-sitosterol; daucosterol; di-(2-ethylhexyl)-phthalate; acetyl aleuritolic acid; 5-methyl-4'-propenoxyanthocyanidines 7-O-β-D-diglucopyranoside.	Guanidine alkaloids and anthocyanidines	Sahu et al. (2012) Agnihotri et al. (2010) Okwu and Ukanwa (2010) Mpiana et al. (2007)
8	*Allium sativum* L. (Alliaceae)	Rhizome	Antimicrobial, antiinflamatory, insecticidal, antifungal, antioxidant	Antisickling suppress hemolysis and reduced membrane deformability	Alliin; allicin; isoalliin; γ-glutamylcysteine peptides; diallyl disulfide; diallyl trisulfide; 3-vinyl-(4H)-1,2-ditiin; 2-vinyl-(3H)-1,3-ditiin; S-methyl cysteine sulfoxide; dimethyl disulfide; dimethyl trisulfide; dimethyl tiosulfonate; sulfur dioxide; alkaloid; tannins; saponin; flavonoids; cardenolides; steroids.	Diallyl disulfide; flavonoids; carotenoids; ascorbic acid.	Otunola et al. (2010)
9	*Aloe barbadensis* Mill. (Liliaceae)	Leaf	Bacteriostatic, wound healing, anticancer	Antisickling	Anthranol; aloe-emodin; chrysophanic acid (chrysophanol); aloin (barbaloin); *p* coumaric acid; aloesin; hydroxyanthraquinones; alkaloids; saponins; tannins phenols; phenylalanine; arginine; tyrosine; aspartic acid; histidine; ascorbic acid; polysacchandes; salicylic acid; vitamins B1, B6, B12	Barbaloin; steroids; acemanna; emodin.	Jain et al. (2011), Okpuzor et al. (2008), Nwaoguikpe et al. (2010), Waller et al. (1978)
10	*Annona senegalensis* Pers. (Annonaceae)	Leaf, bark, root, fruit		Antisickling	Saponins; steroid; flavonoid; glycoside	-	Yisa et al. (2010), Mpiana et al. (2007)

Table 1. Contd.

11	*Bridelia ferruginea* Benth (Euphorbiaceae)	Leaf, stem	Antimicrobial, anti-HIV, antispasmodic, anti-inflammatory, hypoglycemic.	Antisickling	β-amyrin acetate; triterpenes; flavonoids; flavonoid glycosides; rutin; myrcetin derivatives; gallocatechin-(4'-O-7)-epigallocatechin; 3,5-dicaffeoylquinic acid; 1,3,4,5-tetracaffeoylquinic acid; deoxypodophyllotoxin (lignans)	Triterpenes; flavonoids; lignans.	Sahu et al. (2012), Fabiyi et al. (2012), Mpiana et al. (2007, 2009)
12	*Cajanus cajan* (L) Millsp (Fabaceae)	Seed	Antisickling	Sickling reversal, inhibition of sickling, delayed gelation and increase oxygen affinity of HbS, membrane stability	Cajanin; concajanin; 2'-2' methyl cajanone; 2'-hydroxy genistein; isoflavones; orientin; vitexin; isovitexin; pinostrobin; stilbene acid; α-himachalene; β-himachalene; γ-himachalene; α humulene; α-copaene; free p hydroxybenzoic acid; tyrosine; tryptophan; peptides	Phenylalanine; tyrosine; tryptophan; peptides; *p*-hydroxybenzoic acid; cajanin, concajanin, vitexin, isovitexin	Pal et al. (2011), Zu et al. (2010), Wu et al. (2009), Iwu et al. (1988)
13	*Caloncoba welwitschii* (Oliv.) Gilg. (Flacourtiaceae)	Leaf		Antisickling	-	-	Sahu et al. (2012), Mpiana et al. (2007)
14	*Camellia sinensis* (L.) Kuntze (Theaceae)	Leaf	Antioxidant, psoriasis, anticancer, antiobesity	Antisickling	Caffeine; epicatechin; epicatechin-3-gallate; epigallocatechin; epigallocatechin-3-gallate.	Caffeine; epicatechin; epigallocatechin gallate.	Foster (2002), Ohnishi et al. (2001)
15	*Cannabis sativa* L. (Cannabaceae)	Seed, leaf	Antioxidant, analgesic	Analgesic		Caryophylene	Ameh et al. (2012), Lynch et al. (2006)
16	*Carica papaya* L. (Caricaceae)	Unripe fruit,	Antioxidant, antimicrobial	Antisickling and reversal of sickling	Papain; chymopapain; pectin; carposide; carpaine; pseudocarpaine; dehydrocarpines; carotenoids; cryptoglavine; cis-violaxanthin; antheraxanthin; tyrosine; phenylalanine; tryptophan	Tyrosine; phenylalanine; tryptophan; papain; organic acid released from fermentation	Afolabi et al. (2012), Oduola et al. (2006), Thomas and Ajani 1987
17	*Ceiba pentandra* L. (Malvaceae)	Leaf, stem/stem bark, root and whole plant	Antidiabetics, antidiarrhea, Anti-ulcerogenic, Hepatoprotective, Anthelminthic, Hypolipidaemic, Hypoglycaemic	Antisickling	Tannins; flavonoids; glycosides. Vavain glucoside; vavain; flavan-3-ol; (+) catechin	Vavain glucoside; vavain; flavan-3-ol; (+)- catechin	Sahu et al. (2012), Elumalai et al. (2012), Mpiana et al. (2007)
18	*Chenopodium ambrosioides* L. (Chenopodiacea)	Leaf	Antileishmanial, antifungi	Antisickling	Essential oil (α-terpinene, *p*-cymene, ascaridole, and *p*-mentha-1,8-diene)	Ascaridole and *p*-cymene	Sahu et al. (2012), Monzote et al. (2011), Mpiana et al. (2007)
20	*Cissus populnea* Guill. & Perr. (Vitaceae)	Root	Antioxidant	Antisickling	Alkaloids; flavonoids; saponins; tannins; anthraquinone derivatives (physcion and chrysaphanol); steroidal glycosides; cardiac glycosides.	Alkaloids; flavonoids; saponins; tannins.	Soladoye and Chukwuma (2012), Simeone et al. (2012), Moody et al. (2003a)
21	*Citrus sinensis* L. (Rutaceae)	Fruit	Antioxidant	Antisickling	Vitamin C; carotenoid; essential oil (limonene.)	Vitamin C; carotenoids.	Azar et al. (2011), Mpiana et al. (2007)
22	*Coleus kilimandschari* Gurke ex Engl. (Lamiaceae)	Leaf	Antisickling	Antisickling	Coleon U11-acetate; 16-acetoxycoleon U11-acetate; xanthanthusins F-K; coleon U; 8α, 9α-epoxycoleon U-quinone; xanthanthusin E; 14-deoxycoleon U; demethylcryptojaponol; α-amyrin; betulic acid; α-cedrol; β-sitosterol.	coleon U	Sahu et al. (2012), Mpiana et al. (2007)
23	*Cymbopogon citratus* (DC ex Nees) Stapf. (Poaceae)	Leaf	Antimicrobial, antitumor, antinociceptic	Reversal of sickled erythrocytes	Essential oil (geranial, neral, myrcene)	Essential oil (citral and terpenes)	Sahu et al. (2012), Negrelle and Gomes (2007)
24	*Cymbopogon densiflorus* Stapf. (Poaceae)	Leaf	Antioxidant, antimicrobial	Reversal of sickled erythrocytes	Essential oil (Trans-*p*-mentha-2,8-dien-1-ol, verbenol, perillyl alcohol, cis-p-mentha-1(7),8-dien-2-ol)	Essential oil	Sahu et al. (2012), Mpiana et al. (2007)

Table 1. Contd.

25	*Cyperus esculentus* L. (Cyperaceae)	Seed	Antimicrobial, anticancer	Antisickling, Antigellation of sickled cells, improved oxidant status of erythrocytes	Amino acids; proteins; lipids; carbohydrates; alkaloids; sterols; resins; cyanogenic glycosides; saponins; tannins	Arginine; lysine; serine.	Nwaoguikpe (2010) Monago and Uwakwe (2009)
26	*Dacryodes edulis* G. Don (Burseraceae)	Fruit and seed	Antioxidant	Antisickling	Saponin alkaloids; tannins; cyanogenic glycosides	-	Sahu et al. (2012), Mpiana et al. (2007)
27	*Detarium microcarpum* Guill. and Perr. (Fabaceae)	Bark	Antioxidant	Anti-anemic	Alkaloid; saponin; tannins; cardiac glycoside	-	Gbadamosi et al. (2013), Mariod et al. (2009)
28	*Enanthia Chlorantha* Olive (Annonaceae)	Leaf	Antimalaria	Antisickling	Co-enzyme Q10; alkaloids; aldehydes/ketones; carboxylic acids; esters; flavonoids; glycosides; phenols; saponins; steroid/triterpenes; tannins.	Co-enzyme Q10	Ejele et al. (2012)
29	*Entandrophragma utile* (Dawe & Sprague) Sprague (Meliaceae)	Bark	Antiulcer, allergenic	Antisickling	Tannins; 7α,20(*S*)-Dihydroxy-4,24(28)-ergostadien-3-one; 2,6-dimethoxy-2,5-cyclohexadiene-1,4-dione	-	Ameh et al. (2012), Adejumo et al. (2011)
30	*Eugenia caryophyllata* (L.) Merr. & Perry (Myrtaceae)	Fruit, Leaf, stalk	Essential oil possesses antimicrobial, antioxidant, antifungal and antiviral activity antiinflammatory, cytotoxic, insect repellent and anaesthetic properties	Antisickling	Esential oil (Eugenol, humullene, cadinene, trans-β-caryophyllene, and caryophyllene oxide, eucalyptol, torreyol, pinene, linalool, Isolimonene, Viridiflorol); tannins (gallotannic acid); flavonoids (eugenin, rhamnetin, and eugenitin); triterpenoids (oleanolic acid, stigmasterol and campesterol); Fixed oil; glycosides; reducing sugars	Eugenol; eugenyl acetate; β-caryophyllene; gallotannic acid.	Singh et al. (2012), Chaieb et al. (2007), Wambebe et al. (2001)
31	*Garcinia kola* Heckel (Clusiaceae)	Seed	Antioxidant	Membrane stability	Kolaviron; biflavonoids; tannins; alkaloids; anthraquinons; saponosids; terpenoïds; steroids; garcioc; garcinal; tocotrienol.	Kolaviron; biflavanone; tannins	Ijomone et al. (2011), Elekwa et al. (2003)
32	*Harungana madagascariensis* (Lam. ex Poir.) L. (Hypericaceae)	Bark	α-glucosidase enzyme inhibition activity	Antisickling	Saponins; tannins; harunganin; harongin anthrone; harunganol B; kenganthranol A; 1,7-dihydroxyxanthone.	Harunganin [(3,8,9-trihydroxy-6-methyl- 4,4,5-tris(3-methylbut-2-enyl)anthracen-1(4H)-one]	Gbadamosi et al. (2012)
33	*Hymenocardia acida* Tul (Euphorbiaceae)	Leaf	Antimicrobial, antisickling	Sickling reversal	Alkaloids; carbohydrates; proteins; fats and oil; saponins; resins; glycosides; flavonoids; carboxylic acid.	-	Simeone et al. (2012), Sahu et al. (2012), Mpiana et al. (2007)
34	*Ipomoea involucrate,* P. Beauv (Convolvulaceae)	Leaf	Antimicrobial, analgesic, spasmolitic, spasmogenic, hypotensive, psychotomimetic and anticancer activities	Antisickling	Alkaloids; phenolics; terpenes; lignans.	-	Simeone et al. (2012), Sahu et al. (2012), Mpiana et al. (2007)
35	*Justicia secunda* Vahl (Acanthacea)	Leaf and Whole plant	Anticancer	Anti-sickling, Stability of red blood cell membrane and inhibition of polymerization of haemoglobin S.	Flavonoids; anthocyanins	Anthocyanins	Corrêa and Alcântara (2012)
36	*Khaya senegalensis* (Desr.) A Juss (Meliaceae)	Stem bark, root	Cytotoxic against Trypanosome	antisickling activity	Anthraquinones; steroidal glycosides; cardiac glycosides; alkaloids; tannins; senegalensions A,B & C.	Limonoids - Senegalensions A,B & C	Sahu et al. (2012), Sofowora (2008), Mpiana et al.(2007), Vanhaelen-Fastre et al. (1999)
37	*Lawsonia inermis* L. (Lythraceae)	Leaf	Immunomodulatory, antidiabetic, Hepatoprotective, antioxidant, antibacterial, antifungi, antitubercular, cytotoxicity, antifertility, analgesic, molluscicidal, antiviral, abortifacient, antisickling, anticoagulant, wound healing, nematicidal, antimalarial	Antisickling, increase the oxygen affinity of HbSS blood	Lawsone (2- hydroxy-1:4 napthaquinone); gallic acid; glucose; mannitol; fats; resin; mucilage; and traces of an alkaloid; isoplumbagin; lawsaritol.	2-hydroxy-1,4-napthaquinone; isoplumbagin	Chaudhary et al. (2010), Chang and Suzuka (1982)
38	*Mangifera indica* Linn. (Anacardiaceae)	Bark		Anti-anemic	Anthraquinones, alkaloid, saponin, tannins, cardiac glycoside	Limonoid	Gbadamosi et al. (2013)

Table 1. Contd.

39	*Morinda lucida* Benth (Rubiaceae)	Leaf	Antimalarial, antidiabetic, antihypertensive, antimicrobial, Antispermatogenic, Antioxidant	Antisickling	Digitolutein, rubiadin 1-methyl ether, damnacanthal, alkaloids-anthraquinones and anthraquinol.	Alkaloids, anthraquinones and anthraquinol, phenolics	Mpiana et al. (2010, 2007)
40	*Parquetina nigrescens* L. (Asclepiadaceae)	Leaf and stem	Antisickling, antioxidant	Anti-anemic	Anthraquinones, alkaloid, saponin, tannins, cardiac glycoside, amino acids, vit.,B&C, folic acid.	amino acids	Gbadamosi et al. (2012)
41	*Pelargonium xasperum* Enrh. Ex Willd. (Geraniaceae)	Aerial part	Antioxidant	Sickling reversal, inhibit platelet aggregation	Flavonoids	Quercetin; kaempferol	Tzeng et al. (1991), Kokklou and Souleles (1988)
42	*Persia Americana* Mill. (Lauraceae)	Fruit juice	Antioxidant	Antisickling	Phenols; saponins; flavonoids, alkaloid; sterols	Isorhamnetin luteolin; rutin; quercetin; apigenin.	Sahu et al. (2012), Arukwe et al. (2012), Owolabi et al. (2010)
43	*Petiveria alliacea* L. (Phytolaccaceae)	Leaf, stem, root, whole plant.	Antioxidant, antimicrobial	Antisickling	Benzaldehyde; benzoic acid; benzyl 2-hydroxyethyl trisulphide; coumarin; isoarborinol; isoarborinol acetate; isoarborinol cinnamate; isothiocyanates; polyphenols; senfol; tannins; trithiolaniacine; S-phenylmethyl-L-cysteine sulfoxides (petiveriins A and B); S-(2 hydroxyethyl)-L-cysteines (6- hydroxyethiins A and B).	C sulfoxides; benzaldehyde; benzoic acid.	Sahu et al. (2012), Kubec et al. (2002), Kubec and Musah (2001)
44	*Pfaffia paniculata* Pedersen. (Amaranthaceae)	Root	Antisickling, analgesic, anti-arthritic, antitumor, anti- inflammatory, sexual stimulant, increase blood circulation, increase oestrogen production	Anti-anaemia antisickling,	Anthraquinones; aurone; betacyanins; betaxanthins; betalains; chromoalkaloids; ecdysteroids; flavonoids; protoalkaloids; saponins; steroids; triterpenes; zinc; iron; germanium; vitamins. 20-hydroxyecdysone-20,22-monoacetonide; oleanolic acid 3-O-β-D glucuronopyranoside-methyl ester; oleanolic acid 3-O-β-D-glucuro-nopyranoside; oleanoic acid 28-O-β-D-glucopyranosyl ester 4-hydroxy-3-methoxy-benzoicacid; stigmasteryl-3-O-β-D-glucoside; β- sitosterol; daucosterol	Zinc; iron; germanium; allantoin; ecdysteroids; pfaffic acid; pfaffic acid glycosides; saponins; stigmasterol; sitosterol.	Mpiana et al. (2007), Gosmann et al. (2003), Mazzanti and Braghiroli (1994)
45	*Phyllanthus amarus* Schum. (Euphorbiaceae)	Leaf, seed	Antiviral, anti-inflammatory, anticancer, antidiabetic, anti-hypertensive, antimicrobial, improve libido and reproductive function in men.	Antisickling	Flavonoids; tannins; alkaloids; terpenoids; steroids; saponins; cardiac glycosides	-	Obianume and Uche (2009), Mpiana et al. (2007)
46	*Piper guineensis Schum. & Thonn (*Piperaceae*)*	Fruit	Pesticidal, insecticidal or insecticide synergists, antifungal, antimicrobial, anti-tumour, hypotension, bradycardia, immunomodulatory, antiulcerogenic, contraceptive, central nervous system depression, analgesic, antipyretic, anti-inflammatory, and antioxidant	Antisickling	Piperine; wisanine; dihydrocubebin; guineensine; dihydropiperlonguminine; sesamin; trichistachine; piperlonguminin	Piperine.	Okwute and Egharevba (2013), Ameh et al. (2012), Ekanem et al. (2010), Iyamu (2003, 2002), Wambebe et al. (2001)
47	*Plumbago zeylanica* L. (Plumbaginaceae)	Root, whole plant	Antimicrobial, antimicotic, antiplasmodic, antiviral, anticancer, antioxidant	Antisickling	Anthraquinones; flavonoids; saponins; tannins.3-biplumbagin; chloroplumbagin; chitranone; elliptone; 5-methoxyseselin; suberosin; xanthyletin; 2,2-dimethyl-5-hydroxy-6-acetylchromene; plumbagin acid; β-sitosterol; β-sitosteryl-glucoside; bakuchiol; 12-hydroxyisobakuchiol; saponaretin; isoorientin; isoaffinetin; psorealen	Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone)	Adejumo et al. (2010), Vijayakumar et al. (2006), Zhao and Lu (2006), Wang and Huang (2005), Lin et al. (2003), Vander and Lotter (1971)

Table 1. Contd.

48	*Pterocarpus osun* Craib.(Papilionaceae)	Stem	Antimicrobial, antifungal, antioxidant, antisickling	Antisickling	Tannins; saponins; flavonoids; phenols; santalin	Tannins; saponins	Iyamu (2003, 2002), Wambebe et al. (2001)
49	*Pterocarpus santolinoides* DC. (Fabaceae)	Leaf	Analgesic, larvaticidal	Antisickling and increase in gelation time of sickle cell blood	Tannins; flavonoids; terpenoids; steroids; alkaloids; glycosides; saponins; resins	Steroids	Gbadamosi et al. (2012), Anowi et al. (2012), Okpuzor et al. (2008)
50	*Raphia hookeri* Mann and Wendl (Palmaceae)	Stem, Palm sap	Antioxidant, inhibition of RBC polymerization	Inhibits polymerization	4-hydroxybenzoic acid (4-HBA); vitamin C; amino acids; monosaccharides.	4- HBA; flavonoids; thiocyanates; phenylalanine; leucine; arginine; valine.	Ibegbulem et al. (2011)
51	*Senna alata* L. (Fabaceae)	Leaf	Antioxidant, antifungi	Membrane stability	Chrysoeriol; kaempferol; quercetin; emodin; crysophanol; isochrysophanol	Terpenes; sterols; Kaempferol; crysophanol.	Okpuzor et al. (2008)
52	*Senna podocarpa* (Guill. et Perr.) (Fabaceae)	Leaf	Antifungi, antiviral, anticancer, anti-scabies	Membrane stability	Rhein; emodin; chrysophanol; anthraquinones	-	Okpuzor and Adebesin (2006)
53	*Solenostemon monostachyus* P. Beauv. (Lamiaceae)	Leaf	Hypotensive, antioxidant	Antisickling	Flavonoids; coumarin; polyphenol; essential oil.	-	Afolabi et al. (2012)
54	*Sideroxylon puberulum* A. DC. (Sapotaceae)			Sickling reversal		-	Gurib-Fakim and Sewaj (1992)
55	*Sorghum bicolor* L. Moench (Poaceae)	Leaf, seed	Antioxidant	Antisickling	Cyanides; alkaloids; tannins; carotenoids; cyanogenic glycosides; flavonoids; phenolic acids; chlorophyll (a and b); lycopene; β-carotene; palmitic; stearic; oleic and linoleic acid; histidine; methionine; threonine; isoleucine; phenylalanine; tryptophan; valine; sucrose; lactose; maltose; glucose; galactose; thiamine; riboflavin; niacin; vitamins A; 3-deoxy anthocyanins; cyanogenic glycoside; p-hydroxybenzaldehyde	*p*-hydroxybenz-aldehyde; phenylalanine; tryptophan	Abugri et al. (2013), Singh et al. (2012), Chaieb et al. (2007), Wambebe et al. (2001)
56	*Sphenocentrum jollyanun* Pierre (Menispermaceae)	Leaf	Anti-inflammatory	Antisickling		Furanoditerpene	Moody et al. (2003b)
57	*Stephania cepharantha* Hayata (Menispermaceae)		Antipsychotic, inhibit calmodulin-stimulated phosphodiesterase	Sickling reversal, antisickling, delay gelation of HbS	Cepharantine	Cepharantine	Sato and Ohnishi (1982)
58	*Terminalia catappa* L. (Combretaceae)	Leaf	Antioxidant, antibacterial, anti-inflammatory, analgesic, aphrodisiac	Antisickling	Tannin (catappanin A; punicalagin; punicalin; terflavins A & B; tergallagin; tercatain; chebulagic acid; geraniin; granatin B; corilagin); Flavonoids (isovitexin; vitexin; isoorientin; rutin); triterpeniods (ursolic acid; Asiatic acid; 2α, 3β, 23-trihydroxyurs-12en-28-oic acid); phenol glycosides; ascorbic acid; β-carotene; α-tocopherol; p-hydroxybenzoic acid; m-coumaric acid; 3,4-dihydroxybenzoic acid; p-coumaric acid; gallic acid; squalene.	p-hydroxybenzoic acid; m-coumaric acid; 3,4-dihydroxybenzoic acid; p-coumaric acid	Moody et al. (2003a)
59	*Tetracera alnifolia* L. (Dilleniaceae)	Bark	Anticlastogenic, antioxidant, anti-inflammatory, antimicrobial, antidiabetic	Anti-anemic	Saponin; cardiac glycoside.	-	Gbadamosi et al. (2012), Muhammad and Mudi (2011)
60	*Tetracera potatoria* L. (Afzel. ex G. Don) (Dilleniaceae)	Leaf	Antiulcer, antifungal, antioxidant –increase superoxide dismutase activity		Flavonoids; saponins; cardiac glycoside		Gbadamosi et al. (2012), Oluwole et al. (2008)
61	*Theobroma cacao* L. (Malvaceae)	Stem bark	Antioxidant		Polyphenolic; Saponin; cardiac glycoside	Catechins; anthocyanins; proanthocyanidins	Gbadamosi et al. (2012)

Table 1. Contd.

62	*Trema orientalis* L. (Willd.) (Ulmaceae)	Stem bark, root bark	Antidiabetic	Anti-anemic	Alkaloid; saponin; tannins; cardiac glycoside; Methylswertianin; decussating; decussatin glycosides; sweroside; scopoletin; (-)-epicatechin; lupeol; p-hydroxybenzoic acid; 3,4-dihydroxy benzoic acid; adian-5-en-3-one; β-sitosterol; 3-O-β-glucopyranosyl-β-sitosterol; hexacosanoic acid; (–)-ampelopsin F; (+)-catechin; (+)-syringaresinol; N-(trans-p-coumaroyl)tyramine; N-(trans-p-coumaroyl)octopamin; trans-4-hydroxy- cinnamic acid ; 3,5-dimethoxy-4-hydroxyphenyl-1-O-β-D-glucoside; orientoside A.	-	Gbadamosi et al. (2012), Kuo et al. (2007), Tchamo et al. (2001)
63	*Uvaria chamae* P. Beauv (Annonaceae)	Root	Antimicrobial, antioxidant	Antisickling - osmotic resistance	Cardiac glycosides; alkaloids; Oil (thymoquinoldimethyl ether and benzyl benzoate); Chamuvaritin; uvarinol.	Chamuvaritin; uvarinol	Gbadamosi et al. (2012), Okwu and Iroabuchi (2009)
64	*Vanilla planifolia* (Jacks) Andrews (Orchidaceae)	Fruit		Inhibit gelation of HbS, increase oxygen affinity	O-vanillin	O-vanillin	Abraham et al. (1991), Zaugg et al. (1977)
65	*Vernonia amygdalina* Del. (Asteraceae)	Leaf	Antimalarial, antidiabetic, antioxidant	Antisickling	Vitamin C; riboflavin; n-Hexadecanoic acid; stigmasterol; chondrillasterol; Succinic acid; vernodalinol; cynaroside; Stigmasterol; docosanoic acid; uracil; edotides; steroid glucosides.	Saponins; alkaloids; terpenes; steroids; coumarins; phenolic acids; lignans; xanthones	Gbadamosi et al. (2012)
66	*Vigna subterranean* L. Verde. (Fabaceae)	Seed	Antioxidant	Sickling inhibition, sickling reversal, and delay polymerization	Flavonoids; saponins; carbohydrates; fats and oil; resins; terpenoids; steroids; glycosides; alkaloids; proteins.	-	Simeone et al. (2012)
67	*Vigna unguiculata* L. Walp (Fabaceae)	Seed		Sickling inhibition, sickling reversal, and delay polymerization	Saponins; reducing sugar; carbohydrate; fats and oil; steroids; glycosides; alkaloids; proteins	-	Simeone et al. (2012), Sahu et al. (2012), Mpiana et al. (2007)
68	*Vinca minor* L. (Apocynaceae)			Sicking reversal, antisickling	Vincamine; cromesilic acid.	Vincamine; cromesilic acid.	Cabannes et al. (1975)
69	*Waltheria indica* L. (Sterculiaceae)	Leaf	Antibacterial	Antianemic	Anthraquinones; saponins; tannins, cardiac glycoside	-	Gbadamosi et al. (2012)
70	*Zanthoxylum macrophylla* Oliver (Rutaceae)	Root	Antisickling, antibacterial, antiviral, larvicidal, anti-inflammatory, analgesic, antinociceptive, antioxidant, antibiotic, hepatoprotective, antiplasmodial, cytotoxic, antiproliferative, anthelminthic and antifungal	Antisickling	Vanillic acid; *p*-hydroxybenzoic acid; *p*-fluorobenzoic acid; 2-hydroxybenzoic acid; Fagaramide; lupeol	2-Hydroxybenzoic acid; vanillic acid; *p*-hydroxybenzoic acid; *p*-fluorobenzoic acid; Fagaramide; lupeol.	Elekwa et al. (2005), Adesina (2005)
71	*Zanthoxylum zanthoxyloides* (Lam) Waterm. (Rutaceae)	Root, root bark	Antisickling, antibacterial, antiviral, antihepatotoxic, antiallergic, toothache, antitumor and antihypertensive	Antisickling, reversal of sickling	Cardiac glycolsides; alkaloids; saponins; tannins; flavonoids. Divanilloyl quinic acid Pellitorine; fagaronine; 3,4-O-divanilloylquinic acids; 3,5-O-divanilloylquinic acids; 4,5-O-divanilloylquinic acids; 2-hyroxymethyl benzoic acid; 2-hydroxy-3-phenylpropionic acid; vanillic acid; p-coumaric acid; caffeic acid; ferulic acid.	*p*-Hydroxybenzoic acid; zanthoxylol; divanilloyl quinic acid; pellitorine; fagaronine; 2-hyroxymethyl benzoic acid.	Ejele et al. (2012), Ameh et al. (2012), Adegbolagun and Olukemi (2010), Elekwa et al. (2005)

Role of active compounds from medicinal plants used in SCD

The major phytochemicals in plants used for the management of SCD are in Table 1. The classes of these metabolites include phenolics (hydroxybenzoic acids and its derivatives, coumaric acid derivatives, etc.), polyphenolics (flavonoids, anthocyanins, tannins, etc.), anthraquinones, limonoids, alkaloids (urea and guanidine alkaloids, piperidine alkaloids, amide and amine alkaloids, etc.), terpenes (diterpenoids and pentacyclic triterpenoids, etc.) carbohydrates, etc (Figure 2). The activities of some of these plants have been scientifically verified, and the major or active metabolite responsible for the observed activity identified. From the profile of chemicals, it is observed that even those plants not possessing antisickling effect are still very useful as they help to relief pains and probably reduce inflammation and other complications associated with SCD. However, it is obvious that most of the active chemicals have antioxidant activity. Hence, the molecular and metabolic roles of antioxidants in SCD management need to be properly investigated. Amongst plant metabolites, phenolic and polyphenolics are known to possess excellent antioxidant activities, and may play significant role in SCD management.

Free phenolic acids and their derivatives such as, hydroxybenzoic acid and gallate, aromatic amino acids such as phenylalanine, tyrosine and tryptophan, phenylpropanoids such as coumaric acid and its derivatives, are known to possess antisickling activity (Ekeke and Shode, 1990; Dean and Schechter, 1978a, b; Noguchi and Schechter, 1978). Phenylalanine particularly has been found to be a potent inhibitor of HbS gelation and acts by competing for the protein-protein contact sites within the HbS polymer, which may be the mechanism of action of other antisickling amino acids and peptides (Dean and Schechter, 1978a, b; Noguchi and Schechter, 1977). Phenolic acids, such as hydroxybenzoic acid, have been proposed to exhibit their antisickling properties by acting as membrane active agents. The *p*-hydroxybenzaldehyde found in *Sorghum bicolor* L. increases oxygen affinity of HbS as typical of all aldehydes (Beddell et al., 1979). Vanillin, which occurs in over 79 plant genera, is known to inhibit gelation of haemoglobin and markedly increases oxygen affinity of both normal haemoglobin (HbA) and HbS (Sofowora, 2008; Zaugg et al., 1977).

The stilbene, resveratrol, found natural in many plants including peanuts, is believed to be more active as an antioxidant than vitamin C and E (Chanvitayapons et al., 1997). It possesses similar activity to hydroxyurea and acts by inhibiting ribonucleotide reductase and inducing haemoglobin production in the cell (Rodrigue et al., 2001). Resveratrol inhibits lipid peroxidation of LDL and store-operated Ca^{2+} channels (SOCC) thereby preventing Ca^{2+} inflow in thrombin-stimulated human platelet leading to regulated platelet adhesion and intravascular clotting (Dobrydneva et al., 1999; Rotondo et al., 1998; Soleas et al., 1997). Its action has also been linked to inhibition of nitric oxide vascular dependent action in SCA (Bradamante et al., 2003). Thus most plants rich in these simple phenolics may exhibit their pharmacological antisickling property by the synergistic actions of these chemical components.

The naphthoquinone, lawsone, is responsible for the antisickling action of *Lawsonia inermis*. The compound decreases the blood oxygen saturation level required for 50% sickling and lowers the partial pressures at the organs thereby increasing the oxygen affinity of the HbSS red blood cell (Chang and Suzuka, 1982). Plumbagin and other derivatives of naphthoquinones may act in similar manner.

The sesquiterpenoid, β-caryophyllene, the major terpenoid compound found in *Eugenia caryophyllata*, *Canabis sativa*, *Piper guineense* and most essential oils may also possess useful pharmacological activity in SCD management (Ameh et al., 2012). *E. caryophyllata* which is particularly rich in eugenol and β-caryophyllene is an integral part of an active herbal recipe used in the management of SCD. β-Caryophyllene has been found to bind selectively to cannabinoid receptor type 2 (CB_2) which is expressed in the immune system, hematopoietic cells and peripheral nerve terminals where it plays significant role in pain control (Ameh et al., 2012). *C. sativa* seed oil and leaves, richer in β-caryophyllene, are consumed by SCD patients for pain relief in North America (Ameh et al., 2012; Lynch et al., 2006). *C. sativa* has been found to lower intraocular pressure and reduce sleep disturbance by changing blood flow pattern in the brain and limbs, which may be the basis of action in SCD cases (Berlach et al., 2006; Rog et al., 2005; Colasanti, 1986).

Flavonoids include flavones, flavanones, flavanols, isoflavanols/isoflavones, diflavanones, anthocyanins, for example, quercetin, keamferol, apigenin, luteolin, cajanin, rutin, vavain, isohamnetin, etc. The cellular mechanisms of action of bound plasma flavonoids are still not clear. What is clear is that this group of compounds exhibits huge number of biological/pharmacological activities ranging from antioxidant, antipyrectic, anticancer, antiviral, antifungal, antimicrobial to immunomodulatory. Generally, flavoniods are known to act as free radical scavengers, modulator of enzymatic activities, and inhibitor of cellular proliferation, as well as possessing antibiotic, anti-allergenic, anti-diarrheal, anti-ulcer and anti-inflammatory activities. They scavenge peroxyl radicals, alkyl peroxyl radicals, superoxide hydroxyl radicals, and peroxynitrite in aqueous and organic environments, which mitigate against lipid peroxidation,

change in cellular osmotic pressure and subsequent inflammation and cell death (Mira et al., 2002; Nijveldt et al., 2001; Guthrie et al., 2000; Ng et al., 2000; Duthie and Crozier, 2000; Chen et al., 1996; Sanz et al., 1994).

Flavonoids have also been reported to interfere with nitric-oxide synthase reponsibe for the production of nitric oxide which forms peroxynitrite with free radicals. Peroxynitrite can directly oxidize low density lipoproteins (LDLs) resulting in irreversible damage to the cell membrane. Quercetin and some other flavonoids can interfere with xanthine oxidase pathway and help to reduce the generation of superoxide free radicals by the enzymic process. Lipid peroxidation also occurs in the presence of iron and reactive oxygen species. Hence, iron chelators and stabilisers, like quercetin, help to reduce the free radical peroxidation process (Nijveldt et al., 2001). Flavonoids have been shown to decrease adhesion of leukocytes to endothelial wall during ischemia and inflammation reducing the stimulation of degranulation of the neutrophil and enhancing free flow of blood. The inhibitory effect of some flavonoids on mast cell degranulation has been shown to be due to modulation of the receptor-directed Ca^{2+} channels in the plasma membrane (Nijveldt et al., 2001). Flavonoids are believed to be powerful antithrombotic agents *in vitro* and *in vivo* because of their inhibition of the activity of cyclooxygenase and lipoxygenase pathways. It is a known fact that arachidonic acid, which is released in inflammatory conditions, is metabolized by platelets to form prostaglandin, endoperoxides and thromboxane A2, leading to platelet activation and aggregation.

Quercetin and kaempferol inhibit platelet aggregation (Tzeng et al., 1991). The main antiaggregatory effect of flavonoids is thought to be by inhibition of thromboxane A2 formation. Flavonoids affect arachidonic acid metabolism by specifically blocking cyclooxygenase or lipoxygenase, or both enzymes. Most of the activities of flavonoids are believed to be due to the free radical scavenging ability and interference with enzymes functions (Nijveldt et al., 2001). Some of these processes are implicated in metabolism of sickled red blood cells resulting in the observed crises.

Coumarins (phenylpropanoids) derived from a branch of the phenylalanine metabolism pathway that leads ultimately to furanocoumarin (psoralin) synthesis, are another class of bioactive compounds. Although limited data is available to demonstrate the antioxidant activity of coumarins, some of them have been shown to possess anticarcinogenic and antithrombotic activities (Gunatilaka et al., 1994; Fernandez-Puntero et al., 2001; Ng et al., 2000). It is possible that they exhibit their antisikling activity by mimicking the actions of free phenolic acids.

The highly acetylated β (1,4)-linked polysaccharide, acemannan, which is an immunomodulator, antitumor, antiviral and antimicrobial, is believed to act through various mannose mediated mechanisms (Ramamoorthy and Tizard, 1998; Kahlon et al., 1991a, b). The monosaccharides of Acemannan are mannose, glucose and galactose, which are among the eight essential glyconutrients necessary for efficient cell functioning. Acemannan is believed to influence the production of glycoproteins and glucolipids in the liver needed for effective cell communication. Acemannan has been shown to facilitate communication between cells at a distance by stimulating the release of cytokines (Marshall, 1993). It has also been shown to activate macrophages and induce cellular immune response including recognition of foreign antigens (viruses, bacteria and cancer), capture and removal of microorganisms, production of antibody and wound healing. This activity of Acemannan is attributed, in part, to the recognition of terminal mannose by macrophages as a foreign substance (Zhang and Tizard, 1996). The compound has been reported to increase the cytotoxic T-lymphocyte cell in mixed lymphocyte culture (Womble and Helderman, 1992). Thus, much of the activities of the compound as an antiturmor or anticancer, antidiabetes, wound healing, antiviral, antibacterial, anti-psoriasis and immunomodulatory, are primarily through stimulation of glycoprotein and glycolipid levels.

Limonoids are a group of highly oxygenated triterpenoids present mainly in the Rutaceae and Meliaceae families. Research on these compounds has shown that some limonoids could induce the detoxifying enzyme glutathione S-transferase (GST) in the liver of mice and rats (Lam et al., 1989). Hence, limonoids could induce the xenobiotic enzyme, GST, against endogenous peroxide inducing xenobiotics and peroxidized lipids, enabling their ready elimination from the body and prevention of further propagation in the autooxidtion chain-reaction process. Citrus limonoids were also shown to inhibit the formation of chemically-induced neoplasia in the oral cavity, oesophagus or forestomach, small intestine, colon, lung and skin of laboratory animals (Lam et al., 2000; Miller et al., 2000). Limonoids have also been shown to exhibit some antioxidant activity although less than that observed for flavonoids and hydroxycoumarins. They also inhibit the proliferation of breast cancer cells grown in culture (Yu et al., 2005; Tian et al., 2001; Guthrie et al., 2000). Some limonoids are antimalarial and some antimalarials have been reported to be effective in managing SCD (Chikezie et al., 2011, 2010, 2009a, b; Chikezie, 2009, 2008).

Though the link between regional malaria prevalence and SCD prevalence rate has been established and malaria is believed to be worsening SCD prevalence, the molecular relationship between the two diseases is still unclear. High oxygen tension in the blood reduces sickling of HbS but also enhances malaria parasite survival in the red blood cells, while the reverse is also

true. Malaria incidence almost always results in SCD crisis for HbSS patients. The relationship between malaria and SCD crisis may lie in the change in cellular metabolism of HbS erythrocytes and other factors that may affect the immune system of sufferers. More work should be done on the effect of the malaria parasite on HbS erythrocytes and other blood parameters of SCD patient. Rapid breakdown of the RBC by the parasite leading to high concentration of Fe^{2+}, which could act as a prooxidant in the blood could be a factor, and may be accountable for the ability of iron chelators to help reduce crises (Okpuzor et al., 2008).

Most alkaloids, including the piperine and guanidine alkaloids possess a wide range of pharmacological and biological activities, which include anticancer, anti-malarial, antibactierial, antiviral, antifungal, cardiotonic, antidiabetic, antioxidant, immunomodulatory and psyco-active among others (Evans, 2002). Many alkaloids exact their actions by interferance with various enzymic processes although the mechanism of action may differ from one alkaloid to another (Okwute and Egharevba, 2013). For instance, canarosine, a guanidine alkaloid from *Canavalia rosea* DC has been shown to inhibit dopamine D1 receptor binding (Pattamadiloka et al., 2008).

Other compounds from these plants belong to the furano, amides, amino acids, urea, guanidine, cysteine sulfoxide, carotenoid groups. Most of these compounds are rich in pi-electrons and function as antioxidants. It is also possible that some like allantoin which contains the urea moiety, may act by inducing the synthesis of feotal haemoglobin like hydroxyurea or resveratrol. Compounds with the guanidine moiety may exhibit similar action like arginine, while others with amide groups like the piperamides or amide-alkaloids and cysteine sulfoxides, may exhibit actions like the active amino acids such as lysine, arginine and phenylalanine. The furano group appears to be a very potent antioxidant moiety. It is present in 5HMF and ascorbic acid. Hence, it may play a significant role in the activity of the parent compound. It should be noted here however that the actions of most active agents against SCD including hydroxyurea, 5HMF, amino acids etc, are primarily based on their antioxidant property. These compounds which have proven pharmacological activities such as anticancer, antitumor, anti-inflammatory, antibacterial, antimalarial, antifungal, antiviral, antidiabetic, immunomodulatory and antioxidant activity may exhibit most of their activity by free radicals scarvenging and prevention of LDL peroxidation.

CONCLUSION

This review has shown that most well-know anticancer, antitumor, anti-inflammatory, antibacterial, antimalarial, antifungal, antiviral, antidiabetic, immunomodulatory and antioxidant phytochemicals play significant role in ameliorating the SCD crisis. It is time to take a closer look at the interaction between these compounds and the human blood components including the HbS, red blood cells and white blood cell, at the molecular level, with the hope of their possible use in SCD management.

ACKNOWLEDGMENT

The authors acknowledge the Management of the National Institute for Pharmaceutical Research and Development (NIPRD), Idu, Abuja, Nigeria, for its support.

REFERENCES

Abdulmalik O, Osafa MK, Chen Q, Yang J, Brugnara C, Ohene-Frempong K, Abraham DJ, Asakura T (2005). 5-hydroxymethyl-2-furfural modifies intracellular sickle hemoglobin and inhibits sickling of red blood cells. Br. J Haematol. 128(4):552-561.

Abraham DJ, Mehanna AS, Wireko FC, Whitney J, Thomas RO, Orringer EP (1991). Vanillin, a potential agent for the treatment of sickle cell anaemia. Blood 77:1334-1341.

Abreu PM, Noronha RG (1997). Volatile constituents of the rhizomes of *Aframomum alboviolaceum* (Ridley) K. Schum. from Guinea-Bissau. Flav. Frag. J. 12:79-83.

Abugri DA, Tiimob BJ, Apalangya VA, Pritchett G, McElhenney WH (2013). Bioactive and nutritive compounds in *Sorghum bicolor* (Guinea corn) red leaves and their health implication. Food Chem. 138(1):718–723.

Adejumo COE, Kolapo AL, Roleola OP, Kasim LS (2010). In vitro antisickling activities and phytochemical evaluation of *Plumbago zeylanica* and *Uvaria*. Afr. J. Biotechnol. 9(53):9032-9036.

Adejumo OE, Owa-Agbanah IS, Kolapo AL, Ayoola MD (2011). Phytochemical and antisickling activities of *Entandrophragma utile*, *Chenopodium ambrosioides* and *Petiveria alliacea*. J. Med. Plants Res. 5(9):1531-1535.

Adesanya SA, Idowu TB, Elujoba AA (1988). Antisickling activity of *Adansonia digitata.* Planta Med. 54(4):374.

Adesina SK (2005). The Nigerian Xanthoxylum; Chemical and Biological Values. African Journal. Traditional, Complement. Altern. Med. 2(3):282-301.

Afolabi IS, Osikoya IO, Fajimi OD, Usoroh PI, Ogunleye DO, Bisi-Adeniyi T, Adeyemi AO, Adekeye BT (2012). *Solenostemon monostachyus*, *Ipomoea involucrate* and *Carica papaya* (seed oil) versus Glutathione, or *Vernonia amygdalina*: methanolic extract of novel plants for the management of sickle cell anemia disease. BMC Complement. Altern. Med. 12:262.

Agnihotri S, Wakode S, Agnihotri A (2010). An overview on anti-inflammatory properties and chemo-profiles of plants used in traditional medicine. Indian J. Nat. Prod. Resourc. 1(2):150-167.

Ameh SJ, Tarfa FD, Ebeshi BU (2012). Traditional herbal management of Sickle Cell Anemia: Lessons from Nigeria. DOI:10.1155/2012/607436. Anemia p. 9.

Anosike EO, Uwakwe AA, Monanu MO, Ekeke GI (1991). Studies on human erythrocyte glutathione-S transferase from HbAA, HbAS and HbSS subjects. Biochem. Biomed. Acta 50:1051-1055.

Anowi CF, Umeokoli BO, Onyegbule AF, Okonkwo C, Chibeze I (2012). Analgesic, phytochemical and acute toxicity evaluation of the methanol extract of the leaves of *Pterocarpus santalinoides*- Family Fabacea. IJPSR 3(7):2018-2023.

Arukwe U, Amadi BA, Duru MKC, Agomuo EN, Adindu EA, Odika PC, Lele KC, Egejuru L, Anudike J (2012). Chemical composition of *Persea americana* leaf, fruit and seed. IJRRAS 11(2):346-349.

Azar PA, Nekoei M, Larijani K, Bahraminasab S (2011). Chemical composition of the essential oils of *Citrus sinensis* cv. Valencia and a quantitative structure–retention relationship study for the prediction of retention indices by multiple linear regression. J. Serb. Chem. Soc. 76(12):1627–1637.

Beddell CR, Keen G, White RD (1979). The antisickling activity of a series of aromatic aldehydes. Brit. J. Pharmacol. 66:70.

Berlach DM, Shir Y, Ware MA (2006). Experience with the synthetic cannabinoid nabilone in chronic non-cancer pain. Pain Med. 7(1):25-29.

Bradamante S, Barenghi L, Piccinini F, Bertelli AA, Jonge R, de Beemster P, Jong JW (2003). Resveratrol provides late phase cardioprotection by means of nitric oxide- and adenosine-mediated mechanism. Euro J. Pharmacol. 465:115-123.

Brewer GI, Oelshlegel FJ (1974). Antisickling effect of zinc. Biochem. Biophys. Res. Comm. 58: 854-861.

Cabannes R, Cagnard V, Nicolas C, Arne D, Andre AM, Castro JF, Vigneau, Kouassi JC (1975). La drepanocytose/sickle-cell anaemia. Colloquim de l' Institut National de Sante et de Recherche Medical 44:311-320.

Chaieb K, Hajlaoui H, Zmantar T, Kahla-Nakbi AB, Rouabhia M, Mahdouani K, Bakhrouf A (2007). The chemical composition and biological activity of clove essential oil, *Eugenia caryophyllata* (*Syzigium aromaticum* L. Myrtaceae): a short review. Phytother. Res. 21(6):501-506.

Chang H, Ewert SM, Nagel RL (1983). Identification of 2-imidazolines as anti-sickling agents. Am. Soc. Pharmacol. Exp. Therapeut. 23(3):731-734.

Chang H, Suzuka SE (1982). Lawsone derived from the henna. Plant increases the oxygen affinity of sickle cell blood. Biochem. Biophys. Res. Commun. 107:602-608.

Chanvitayapongs S, Draczynska-Lusiak B, Sun SY (1997). Amelioration of oxidative stress by antioxidants and resveratrol in PC 12 cells. Neuroreport 8:1499-1502.

Chaudhary G, Goyal S, Poonia P (2010). *Lawsonia inermis* Linnaeus: A Phytopharmacological Review. IJPSDR 2(2):91-98.

Chen ZY, Chan PT, Ho KY, Fung KP, Wang J (1996). Antioxidant activity of natural flavonoids is governed by number and location of their aromatic hydroxyl groups. Chem. Phys. Lipids 79:157-163.

Chikezie PC (2008). Comparative *in vitro* osmotic stability of three human erythrocyte genotype (HbAA, HbAS and HbSS) in the presence of quinine and chloroquine phosphate. Int. Sci. Res. J. 1(2):135-140.

Chikezie PC (2009). Comparative methaemoglobin concentrations of three erythrocyte genotypes (HbAA, HbAS and HbSS) of male participants administered with five antimalarial drugs. Afr. J. Biochem. Res. 3(6):266-271.

Chikezie PC, Chikezie CM, Amaragbulem PI (2011). Polymerization of human sickle cell haemoglobin (HbS) in the presence of three antimalarial drugs. Afr. J. Biochem. Res., 5(2): 39-42,

Chikezie PC, Chikezie CM, Amaragbulem PI (2010). Effect of antimalarial Drugs on Polymerization of Sickle Cell Hemoglobin (HbS). Turk. J. Biochem. 35(1):41–44.

Chikezie PC, Uwakwe AA, Monago CC (2009a). Glutathione S-transferase activity of three erythrocyte genotypes (HbAA, HbAS and HbSS) of male subjects/volunteers administered with Fansidar and Quinine. Afr. J. Biochem. Res. 3(5):210-214.

Chikezie PC, Uwakwe AA, Monago CC (2009b). Studies of human HbAA erythrocyte osmotic fragility index of non-malarious blood in the presence of five antimalarial drugs. J. Cell Anim. Biol. 3(3):039-043.

Colasanti BK (1986). Review: Ocular hypotensive effect of marihuana cannabinoids: correlate of central action or separate phenomenon. J. Ocular Pharmacol. 2(3):295-304.

Correa GM, Alcântara AFC (2012). Chemical constituents and biological activities of species of *Justicia* - a review. Braz. J. Pharmacogn. 22(1):220-238.

Dean J, Schechter AN (1978a). Sickle cell anaemia: molecular and cellular basis of therapeutic approaches (first of three parts). N. Engl. J. Med. 299:863- 870.

Dean J, Schechter AN (1978b). Sickle cell anemia: molecular and cellular basis of therapeutic approaches (third of three parts). New Engl. J. Med. 229:753-755.

Dobrydneva Y, Williams RL, Blackmore PF (1999). Trans-resveratrol inhibits calcium influx in thrombin-stimulated human platelets. Brit. J. Pharmacol. 128:149-157.

Dong H, Chen SX, Xu HX, Kadota S, Namba T (1998). A new antiplatelet diarylheptanoid from *Alpinia blepharocalyx*. J. Nat. Prod. 61:142-144.

Duthie G, Crozier A (2000). Plant-derived phenolic antioxidants. Curr. Opin. Lipidol. 11:43-47.

Ejele AE, Akpan IO, Ogukwe CE, Onyeocha VO, Ukiwe LN (2012). Bioassay-guided isolation and partial characterization of an antisickling compound from *Enantia chlorantha*. Intern. Res. J. Biochem. Bioinform. 2(7):149-154.

Ekanem AP, Udoh FV, Oku EE (2010). Effects of ethanol extract of *Piper guineense* seeds (Schum. and Thonn) on the conception of mice (*Mus musculus*). Afr. J. Pharm. Pharmacol. 4(6):362-367.

Ekeke GI, Shode FO (1990). Phenylalanine is the predominant antisickling agent in *Cajanus cajan* seed extract. Planta Med. 56:41-43.

Elekwa I, Monanu MO, Anosike EO (2003). Studies on the effects of aqueous extracts of *Garcinia kola* seed on the human erythrocytes adenosine triphosphate of HbAA, HbAS and HbSS genotypes. Global Journal of Medical Sciences, 2(2):107-114.

Elekwa I, Monanu MO, Anosike EO (2005). *In vitro* effects of aqueous extracts of *Zanthxylum macrophyla* roots on adenosine triphosphatases from human erythrocytes of different genotypes. Biokemistri 17(1):19-25.

Elumalai A , Mathangi N, Didala A, Kasarla R, Venkatesh Y (2012). A Review on *Ceiba pentandra* and its medicinal features. Asian J. Pharm. Technol. 2(3):83-86.

Evans WC (2002). Trease and Evans Pharmacognosy, 15th ed., W.B Saunders, Edinburgh; 585pp.

Fabiyi OA, Atolani O, Adeyemi OS, Olatunji GA (2012). Antioxidant and cytotoxicity of β-amyrin acetate fraction from *Bridelia ferruginea* Leaves. DOI: 10.1016/S2221-1691(12)60347-5. Asian Pacific J. Trop. Biomed. pp. S981-S984.

Fernandez-Puntero B, Barroso I, Iglesias I, Benedi J, Villar A (2001). Antioxidant activity of Fraxetin: in vivo and ex vivo parameters in normal situation versus induced stress. Biol. Pharm. Bull. 24:777-784.

Foster S (2002). Green Tea (*Camellia sinensis*). Alternative Medicine Review Monographs, Thorne Inc. pp. 200-204.

Gbadamosi IT, Adeyemi SB, Adeyemi AA, Moody JO (2013). In vitro antisickling activities of two indigenous plant recipes in Ibadan, Nigeria. Int. J. Phytochem. 4(2):205-211.

Gbadamosi IT, Moody JO, Yekini AO (2012). Nutritional composition of ten ethnobotanicals used for the treatment of anaemia in Southwest Nigeria. Euro. J. Med. Plants 2(2):140-150.

Gibson XA, Shartava A, McIntyre J, Monteiro CA, Zhang Y, Shah A, Campbell NF, Goodman SR (1998). The efficacy of reducing agents or antioxidants in blocking the formation of dense cells and irreversibly sickled cells *in vitro*. Blood 91(11):4373–4378.

Gosmann G, Gattuso S, Gattuso M, Fenner R, Pacheco EF, Ferraz A, Savi LA, Barardi CRM, Simões CMO, Sortino M, Zacchino S, Gnerre C, Testa B , Rates SMK (2003). Botanical (morphological, micrographic), chemical and pharmacological characteristics of Pfaffia species (Amaranthaceae) native to South Brazil. Braz. J. Pharmaceut. Sci. 39(2):142-147.

Gunatilaka AA, Kingston DG, Wijeratne EM, Bandara BM, Hofmann GA, Johnson RK (1994). Biological activity of some coumarins from Sri Lankan Rutaceae. J. Nat. Prod. 57:518-520.

Gupta R, Gupta AK, Aiswarya G (2010). Pharmacognostical investigations on *Acacia leucophloea* leaf. Res. J. Pharm. Biol. Chem. Sci. 1(4):360-365.

Gurib-Fakim A, Sewaj MD (1992). Studies on the antisickling properties of extracts of *Sideroxylon puberulum, Fanjariopsis flexuosa,*

Cardispernus halicacabum and *Pelargomium graveolens*. Planta Med. 58:648-649.
Guthrie N, Morley K, Hasegawa S, Manners GD, Van- denberg T (2000). Inhibition of human breast cancer cells by citrus limonoids. In: Citrus limonoids: Functional Chemicals in Agriculture and Foods; Berhow MA, Hasegawa S, Manners GD (Eds). ACS Symposium Series 758, American Chemical Society, Washington DC pp. 164-174.
Ibegbulem CO, Eyong, EU, Essien EU (2011). Polymerization inhibition activity of *Raphia hookeri* palm sap and its effect on osmotic fragility of sickle cell red blood cells. J. Med. Plants Res. 5(17):4212-4217.
Iwu MN, Igboko AO, Onwubiko H, Ndu UE (1988). Effect of *Cajanus cajan* on gelation and oxygen affinity of sickle cell hemoglobin. J. Ethnopharm. 20:99-104.
Iyamu EW, Turner EA, Asakura T (2002). *Invitro* effects of Niprisan (Nix 0699). A natural occurring potent antisickling agent. Br. J. Haematol. 118(1):337-343.
Iyamu EW, Turner EA, Asakura T (2003). Niprisan (Nix-0699) improves the survival rates of transgenic sickle cell mice under acute severe hypoxic conditions. Br. J. Haematol. 122(6):1001–1008.
Jain P, Chouhan P, Shukla RN (2011). Chemical composition of anticancerous component (acemannan and emodin) from *Aloe vera* and dehydration effect of Aloe at different temperature. Alfa Universal, 2(3): 147-157.
Jensen M, Shobet SB, Nathan DG (1973). The role of red cell energy metabolism in the generation of irreversibly sickled cell in vitro. Blood 42:835-842.
Kahlon J, Kemp M, Yawei N, Carpenter RH, Shannon WM, McAnalley BH (1991a). *Invitro* evaluation of the synergistic antiviral effects of acemannan in combination with azidothymidine and acyclovir. Mol. Biother. 3(4):214-223.
Kahlon JB, Kemp MC, Carpenter RH, McAnalley BH, McDaniel HR, Shannon WM (1991b). Inhibition of AIDS virus replication by acemannan *in vitro*. Mol. Biother. 3(3):127-135.
Koch AA, Olney RS, Yang Q (2002). Sickle hemoglobin allele and Sickle Cell Disease. Am. J. Epidemiol., 9: 839-845.
Kokkalou E, Souleles C (1988). Flavonoid constituents of *Pelergonium xasperum* Enrh. Ex Willd. Geraniaceae. Plantes Med. Phytother. 22:247-253.
Kubec R, Kim S, Musah RA (2002). "S-Substituted cysteine derivatives and thiosulfinate formation in *Petiveria alliacea*-Part II". Phytochem. 61:675–680.
Kubec R, Musah RA (2001). "Cysteine sulfoxide derivatives in *Petiveria alliacea*". Phytochem. 58:981–985.
Kuo WL, Huang YL, Wang ST, Ni CL, Shien BJ, Chen CC (2007). Chemical constituents of *Trema orientalis*. J. Chin. Med. 18(1, 2):27-36.
Lam LKT, Hasegawa S, Bergstorm C, Lam SH, Kenney P (2000). Limonin and nomilin inhibitory effects on chemical-induced tumorigenesis. In: Citrus Limonoids: Functional Chemicals in Agriculture and Foods; Berhow MA, Hasegawa S, Manners GD, (Eds).; ACS Symposium Series 758, American Chemical Society, Washington DC. pp. 185-200.
Lam LKT, Li Y, Hasegawa S (1989). Effects of citrus limonoids on glutathione S-transferase activity in mice. J. Agric. Food Chem. 37:878-880.
Li X, Wang H, Liu C, Chen R (2010). Chemical constituents of *Acacia catechu*. Zhongguo Zhong Yao Za Zhi 35(11):1425-1427.
Lin LC, Yang LL, Chou CJ (2003). Cytotoxic naphthoquinones and plumbagic acid glycosides from *Plumbago zeylanica*. Phytochemistry 62(4):619-622.
Lynch ME, Young J, Clark AJ (2006). A case series of patient using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulation. J. Pain Sympt. Manage. 32(5):497-501.
Malviya S, Rawat S, Kharia A, Verma M (2011). Medicinal attributes of *Acacia nilotica* Linn. - A comprehensive review on ethnopharmacological claims. Int. J. Pharm. Life Sci. 2(6):830-837.
Mariod AA, Mirghani MES, Abdul AB, Abdelwahab SI (2009). *Detarium microcarpum* Guill and Perr fruit proximate chemical analysis and sensory characteristics of concentrated juice and jam. Afr. J. Biotechnol. 8(17):4217-4221.
Marlier M, Guellec GL, Lognay G, Wathelet JP, Severin M (1993). Characterization of three Labdane Diterpenes from *Aframomum alboviolaceum*. Planta Med. 59(5):455-457.
Marshall G (1993). Paper presented at: American Aging Association's 23rd Annual Meeting; 1993/10/08.
Martin DW (1983). Structure and function of a protein – haemoglobin. In: Martin DW, Mayes PA, Rodwell VW (eds). Harper's Review of Biochemistry. 9th Edition. Lange Medical Publications. California.
Mazzanti G, Braghiroli L (1994). Analgesic, anti-inflammatory action of *Pfaffia paniculata* (Martius) Kuntze. Phytother. Res. 8:413-416.
McGoron AJ, Joiner CH, Palascak MB, Claussen WJ, Franco RS (2000). Dehydration of mature and immature sickle red blood cells during fast oxygenation/deoxygenation cycles: role of KCL cotransport and extracellular calcium. Blood 95:2164-2168.
Mehanna AS (2001). Sickle cell anemia and antisickling agents then and now. Curr. Med. Chem. 8(2):79-88.
Miller EG, Taylor SE, Berry CW, Zimmerman JA, Hasegawa S (2000). Citrus limonoids: increasing importance as anticancer agents. In: Citrus Limonoids: Functional Chemicals in Agriculture and Foods; Berhow MA, Hasegawa S, Manners GD (Eds.); ACS Symposium Series 758, American Chemical Society, Washington, DC. pp. 132-144.
Mira L, Fernandez MT, Santos M, Rocha R, Florencio MH, Jennings KR (2002). Interactions of flavonoids with iron and copper ions: a mechanism for their antioxidant activity. Free Rad. Res. 36:1199-208.
Monago CC, Uwakwe AA (2009). Proximate composition and in-vitro anti sickling property of Nigerian *Cyperus esculentus* (tiger nut sedge). Trees Life J. 4(2):1-6.
Monzote L, Nance MR, García M, Scull R, Setzer WN (2011). Comparative chemical, cytotoxicity and antileishmanial properties of essential oils from *Chenopodium ambrosioides*. Nat. Prod. Commun. 6(2):281-286.
Moody JO, Ojo O, Omotade OO, Adeyemo AA, Olusese PE, Ogundipe A (2003a). Anti-sickling potential of a Nigerian herbal formular and the major plant component *Cissus populnea* L. CPK. Phytother. Res. 10:1137–1176.
Moody JO, Robert VA, Connolly JD, Houghton PJ (2003b). Anitinflammatory activities of methanol extracts and an isolated furanoditerpene constituent of *Sphenocentrum jollyanum* Pierre (Menispermaceae). J. ethnopharmacol. 104(1-2):67-91.
Mpiana PT, Ngbolua Koto Te Niwa N, Bokota MT, kasonga TK, Atibu EK, Tshibangu DST, Mudogo V (2010). Invitro effects of anthocyanin extracts from *Justicia secunda* Vahl on the solubility of Haeemoglobin S and membrane stability of sickle erythrocytes. Blood Transfus., 8(4): 248-254. Doi: A 10- 2450/ 2009. 0120- 09, PMID: PMC. 2957489.
Mpiana PT, Tshibangu DST, Shehonde OM, Ngbolua KN (2007). *In-vitro* antidrepanocytary activity (antisickle cell anaemia) of some Congolese plants. Phytomedicine 14(2-3):192 - 195.
Muhammad A, Mudi SY (2011). Phytochemical Screening and Antimicrobial Activities of *Terminalia catappa*, leaf Extracts. Biokemistri 23(1):35-39.
Nagalla S, Ballas SK (2010). Drugs for preventing red blood cell dehydration in people with sickle cell disease. The Cochrane Collaboration, John Wiley & Sons, Ltd., 1:28.
Negrelle RRB, Gomes EC (2007). *Cymbopogon citratus* (DC.) Stapf: chemical composition and biological activities. Rev. Bras. Pl. Med., Botucatu 9(1):80-92.
Ng TB, Liu F, Wang ZT (2000). Antioxidative activity of natural products from plants. Life Sci. 66:709-723.
Nijveldt RJ, van Nood E, van Hoorn DEC, Boelens PG, van Norren K, van Leeuwen PAM (2001). Flavonoids: a review of probable mechanisms of action and potential applications. Am. J. Clin. Nutr. 74:418–25.
Noguchi CT, Schechter AN (1978). Inhibition of gelation by amino acids and related compounds. Biochemistry 17:5455-5459.

Nwaoguikpe RN, Braide W, Ezejiofor TIN (2010). The effect of aloe vera plant (*Aloe barbadensis*) extracts on sickle cell blood (HbSS). Afr. J. Food Sci. Technol. 1(3):058-063.
Nwaoguikpe RN (2010). The phytochemical, proximate and amino acid compositions of the extracts of two varieties of tiger nut (*Cyperus esculentus*) and their effects on sickle cell hemoglobin polymerization. J. Med. Med. Sci. 1(11):543-549.
Obianime AW, Uche FI (2009). The Phytochemical constituents and the effects of methanol extracts of Phyllanthus amarus leaves (kidney stone plant) on the hormonal parameters of Male guinea pigs. J. Appl. Sci. Environ. Mgt. 13(1):5-9.
Obodozie OO, Ameh SJ, Afolabi EK, Oyedele EO, Ache TA, Onanuga CE, Ibe MC, Inyang US (2009). Standardization of the components of niprisan: A phytomedicine for treating sickle cell disease. J. Med. Plants Res. 3(4):284-289.
Oduola T, Adeniyi FAA, Ogunyemi EO, Bello IS, Idowu TO (2006). Antisickling agent in an extract of unripe pawpaw (*Carica papaya*). Afr. J. Biotechnol. 5(20):1947-1949.
Ohnishi ST, Ohnishi T, Ogunmola GB (2001). Green tea extract and aged garlic extract inhibit anion transport and sickle cell dehydration in-vitro. Blood Cells Molec. Dis. 27:148-157.
Okpuzor J, Adebesin O (2006). Membrane stabilizing effect and antisickling activity of S*enna podocarpa* and *Senna alata*. 31st congress for European biochemical societies, Instanbul, Turkey pp. 25-29.
Okpuzor J, Adebesin O, Ogbunugafor H, Amadi I (2008). The potential of medicinal plants in sickle cell disease control: A review. Int. J. Biomed. Health Sci. 4(2):47-55.
Okwu DE, Iroabuchi F (2009). Phytochemical composition and biological activities of *Uvaria chamae* and *Clerodendoron splendens*, E-J. Chem. 6(2):553-560
Okwu DE, Ukanwa N (2010). Isolation, characterization and antibacterial activity screening of anthocyanidine glycosides from *Alchornea cordifolia* (Schumach. And Thonn.) Mull. Arg. leaves. E-J. Chem. 7(1):41-48.
Okwute SK, Egharevba HO (2013). Piperine-Type Amides: Review of the Chemical and Biological Characteristics. DOI:10.5539/ijc.v5n3p99. Int. J. Chem. 5(3):99-122.
Oluwole FS, Ayo JA, Omolaso BO, Emikpe BO, Adesanwo JK (2008). Methanolic Extract of Tetracera potatoria, an Antiulcer Agent Increases Gastric Mucus Secretion and Endogenous Antioxidants. Niger. J. Physiol. Sci. 23(1-2):79-83.
Otunola GO, Oloyede OB, Oladiji AT, Afolayan AJ (2010). Comparative analysis of the chemical composition of three spices – *Allium sativum* L., *Zingiber officinale* Rosc. and *Capsicum frutescens* L. commonly consumed in Nigieria. Afr. J. Biotechnol. 9(41):6927-6931.
Owolabi MA, Coker HAB, Jaja SI (2010). Bioactivity of the phytoconstituents of the leaves of Persea Americana. J. Med. Plants Res., 4(12): 1130-1135. DOI: 10.5897/JMPR09.429
Pal D, Mishra P, Sachan N, Ghosh AK (2011). Biological activities and medicinal properties of *Cajanus cajan* (L) Millsp. DOI: 10.4103/2231-4040.90874. J. Adv. Pharm. Technol. Res. 2(4):207–214.
Pattamadiloka D, Pengsuparpb T, Phummiratchb D, Ongpipattanakulb B, Meksuriyenb D, Kawanishic K, Kanedac N, Suttisria R (2008). Canarosine: A new guanidine alkaloid from *Canavalia rosea* with inhibitory activity on dopamine D1 receptors. J. Asian Nat. Prod. Res. 10(10):915–918.
Ramamoorthy L, Tizard IR (1998). Induction of apoptosis in a macrophage cell line RAW 264.7 by acemannan, a beta-(1,4)-acetylated mannan. Mol. Pharmacol. 53(3):415-421.
Rog DJ, Nurmikko TJ, Friede T, Young CA (2005). Randomised controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65(6):812-819.
Rotondo S, Rajtar G, Manarini S, Celardo A, Rotillo D, de Gaetano G, Evangelista V, Cerletti C (1998). Effect of transresveratrol, a natural polyphenolic compound on human polymorphonuclear leukocyte function. Br. J. Pharmacol. 123:1691-1699.
Sahu M, Singh V, Yadav S, Harris KK (2012). Plant extracts with antisickling propensities: a feasible succor towards sickle cell disease management- a mini review. J. Phytol. 4(3):24-29.
Sanz MJ, Ferrandiz ML, Cejudo M, Terencio MC, Gil B, Bustos G, Ubeda A, Gunasegaran R, Alcaraz MJ (1994). Influence of a series of natural flavonoids on free radical generating systems and oxidative stress. Xenobiotica 24:689-699.
Sato T, Ohnishi ST (1982). *In vitro* antisickling effect of cepharantine. Eur. J. Pharmacol. 83:91-95.
Sauntharajah Y, Molokie R, Saraf S, Sidhwani S, Gowhar M, Vara S, Lavelle D, DeSimone J (2008). Clinical effectiveness of decitabine in severe sickle cell disease. Br. J. Haematol. 141(1):126-129.
Simeone EI, Tufon EN, Victor ON, Noel NN (2012). Antisickling potential of the ethanol seed extracts *of Vigna unguiculata* and *Vigna subterranean*. Int. J. Biochem. Biotechnol. 1(9):226-229.
Singh J, Baghotia A, Goel SP (2012). *Eugenia caryophyllata* Thunberg (Family Myrtaceae): A Review. IJRPBS. 3(4):1469-1475.
Sofowora A (2008). Medicinal plants and traditional medicine in Africa. Spectrum books limited Ibadan. pp. 356-374.
Soladoye MO, Chukwuma EC (2012). Phytochemical analysis of the stem and root of *Cissus populnea* (Vitaceae) – an important medicinal plant in Central Nigeria. Phytol. Balcanica 18(2):149-153.
Soleas GJ, Diamandis EP, Goldberg DM (1997). Resveratrol, a molecule whose time has come/ and gone. Clinical Biochem., 30: 91-113.
Stocker JW, De Franceschi L, McNaughton-Smith G, Corrocher R, Beuzard Y, Brugnara C (2003). ICA-17043, a novel Gardos channel blocker prevents red blood cell dehydration *invitro* and *invivo* SAD mice. Blood, 101(6): 2412-2418.
Sulaiman CT, Gopalakrishnan VK (2013). Radical scavenging and in-vitro Hemolytic Activity of Aqueous Extracts of Selected *Acacia* Species. J. Appl Pharmaceutical Sci., 3(03): 109-111.
Tchamo DN, Cartier G, Dijoux-Franca MG, Tsamo E, Mariotte AM (2001). Xanthones and Other Constituents of *Trema orientalis*. Pharmaceutical Biol., 39(3): 202–205.
Thomas KD, Ajani B (1987). Antisickling agent in an extract of unripe pawpaw fruit (*Carica papaya*). Transactions Royal Soc. Trop Med & Hyg. 81: 510-511.
Tian QG, Miller EG, Ahmad H, Tang L, Patil BS (2001). Differential inhibition of human cancer cells proliferation by citrus limonoids. Nutr. Cancer, 40: 180-184.
Tzeng SH, Ko WC, Ko FN, Teng CM (1991). Inhibition of platelet aggregation by some flavonoids. Thrombosis Res., 64: 91-100.
Uzoegwu PN, Onwurah AE (2003). Correlation of lipid peroxidation index with sickle haemoglobin concentrations in malarial-positive, -negative statuses of AA, AS and SS individuals from the University of Nigeria, Nsukka community. J. Biol. Res. Biotech., 1(1): 97-114.
Vander VLM, Lotter AP (1971). The constituents in the roots of *Plumbago auriculata* Lam. and *Plumbago zeylanica* L. responsible for antibacterial activity. Planta Med., 20: 8-13.
Vanhaelen-Fastre R, Vahaelen M, Lo I, Toppet M, Ferster A, Fondu P (1999). In vitro antisickling activity of a rearranged limonoid isolated from *Khaya senegalensis*. Planta Med., 65(3): 209-212.
Vijayakumar R, Senthilvelan M, Ravindran R, Devi RS (2006). *Plumbago zeylanica* action on blood coagulation profile with and without blood volume reduction. Vascul Pharmacol., 45(2): 86-90.
Wainscoat JS (1987). The origin of mutant globin genes in human population . Acta . Haematol., 78: 154-158.
Waller GR, Mangiafico S, Ritchey CR (1978). A chemical investigation of *Aloe barbadensis* MILLER. Proc. Okla. Acad. Sci. 58: 69-76.
Wambebe C, Khamofu H, Momoh JA, Ekpeyong M, Audu BS, Njoku SO, Nasipuri NR, Kunle OO, Okogun JI, Enwerem NM, Gamaniel SK, Obodozie OO Samuel B, Fojule G, Ogunyale PO (2001). Double-blind, placebo-controlled, randomised cross-over clinical trial of NIPRISAN in patients with sickle cell disorder *Phytomedicine*, 8(4):252-61.
Wang YC, Huang TL (2005). High-perfomance liquid chromatography for quantification of plumbagin an anti-*Helicobacter pylori* compound of *Plumbago zeylanica*. J. Chromatogr. A, 1094: 99-104.
Weatheral DJ, Abdalla SH, Pippard K (1983). The anaemia of *Plasmodium falciparum* malaria. In: malaria and the red cell. Ciba

Symposium, London. Pitman., 94: 74-88.
Womble D, Helderman J (1992). The impact of acemannan on the generation and function of cytotoxic T-lymphocytes. Immunopharmacol Immunotoxicol, 14(1-2): 63–77.
Wu N, Fu K, Fu YJ, Zu YG, Chang FR , Chen YH , Liu XL , Kong Y, Liu W, Gu CB (2009). Antioxidant activities of extracts and main components of Pigeon pea [*Cajanus cajan* (L.) Millsp.] DOI: 10.3390/molecules14031032. leaves. Mol. 14:1032-1043.
Yisa J, Egila JN, Darlinton AO (2010). Chemical composition *of Annona senegalensis* from Nupe land, Nigeria. Afr. J. Biotechnol. 9(26):4106-4109.
Yu J, Wang L, Walzem RL, Miller EG, Pike LM, Patil BS (2005). Antioxidant Activity of Citrus Limonoids, Flavonoids, and Coumarins. J. Agric. Food Chem. 53(6):2009-2014.
Zaugg RH, Walder JA, Koltz IM (1977). Schiff base adducts of haemoglobin: modifications that inhibit erythrocyte sickling. J. Biol. Chem. 252:8542-8548.
Zhang L, Tizard IR (1996). Activation of a mouse macrophage cell line by acemannan: The major carbohydrate fraction from *Aloe vera* gel. Immunopharmacol. 35(2):119-128.
Zhao YL, Lu DP (2006). Effects of plumbagin on the human acute promyelocytic leukaemia cells in vitro. Zhongguo Shi Yan Xue Ye Xue Za Zhi 14(2):208-211.
Zu YG, Liu XL, Fu YJ, Wu N, Lui W, Kong Y, Wink M (2010). Chemical composition of the SPE-CO extracts from *Cajanus cajan* (L.) Huth and their antimicrobial activity *invitro* and *invivo*. Phytomed. 17:1095-1101.