HSI Health Sciences Investigations Journal

share

Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

ISSN Online 2704-4890 | ISSN Print 2720-7609

Online first publication

Review Article

HSI Journal (2024) Volume 6 (Issue 2):990-1113. https://doi.org/10.46829/hsijournal.2024.12.6.2.990-1013

Open Access

The efficacy of herbal medicines used in the management of sickle cell disease: a systematic review of two randomised control studies

Effah RA POMAA [1], Jospeh ANSAH [2], Bariya M NORGAH [3], Samuel ANKAMAH [4], Naomi AMOFAH-SERWAA [4], Emmanuel A PREMPEH [3], Emelia OPPONG BEKOE [3*]

[1] University of Ghana Medical Center, Accra, Ghana; [2] Department of Pharmacy Practice and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, University of Ghana, Accra, Ghana; [3] Department of Pharmacognosy and Herbal Medicine, School of Pharmacy, College of Health Sciences, University of Ghana, Accra, Ghana; [4] University of Ghana Library System, University of Ghana, Accra, Ghana

Received September 2024; Revised October 2024; Accepted December 2024

Abstract

Background: Over 300,000 babies are born with the severe form of sickle cell disease (SCD) worldwide, with most occurring in low- and middle-income countries. Although the pathophysiology of this disease is now better understood, there are still few conventional pharmacological treatments available, with these medicines having adverse effects that affect compliance. Various herbal remedies have been employed since the discovery of SCD to minimise unpleasant sickling events. Additionally, an increasing number of patients have turned to complementary and alternative medicines (CAM) and naturopathic substances in managing excruciating episodes.

Objective: This mini-systematic review assessed the efficacy of medicinal plants used in the management of SCD.
Method: A web-based literature search was conducted in PubMed, Scopus (Elsevier), Cochrane Library and CINAHL Complete (Ebsco) to obtain randomised controlled studies. Two hundred and five articles were retrieved, of which only two were included in the review.

Results and Concludions: This study found that two phytomedicines, Niprisan® and Ciklavit®, significantly reduced severe pain in patients. The mean frequency of times patients reported severe pains during the 6-month trials was 7.9 for the Niprisan® group and 21.1 for the placebo. After cross-over in the second 6 months, the placebo was 6.9, and Niprisan® was 4.1. Side effects experienced included non-itching macular rashes and headaches. Ciklavit® also reduced painful crises from 207 to 191 with mild side effects, including abdominal distention and tiredness. Niprisan® did not significantly change liver enzyme activity, cause significant differences in jaundice and serum bilirubin, or cause acute liver or renal damage. A significant number of medicinal plants have been documented as folklorically used in managing SCD, its associated pain, and anaemia. These will need in-depth investigations for further advancements. This study highlights the potential benefits of using phytomedicines for the management of SCD.

Keywords: Herbal medicine, naturopathy, sickle cell disease, randomised control trial

Cite the publication as Pomaa ER, Ansah J, Norgah BM, Ankamah S, Amofah-Serwaa N, Prempeh EA, Oppong-Bekoe E (2024) The efficacy of herbal medicines used in the management of sickle cell disease: A systematic review of two randomised control studies. HSI Journal 6 (2):990-1013. https://doi.org/10.46829/hsijournal.2024.12.6.2.990-1013

INTRODUCTION

SCD comprises several disorders identified by the presence of sickle haemoglobin. Two of these variants HbS, and HbC are prevalent in Africa despite the identification of over 700 other haemoglobin variants with most of them not being clinically significant [1]. SCD arises from primarily Hbs substitution mutating on the beta-globulin chain where valine replaces glutamic acid leading to the production of abnormal HbS [2,3]. This recessively inherited haemoglobin disease mainly affects individuals from Sub-Saharan Africa, the Caribbean, South America the Indian Subcontinent, the Middle East and the Mediterranean Basin [4]. Although the pathophysiology of SCD is now better understood, there are still just a few pharmacological treatments available [5]. SCD can only be cured by bone marrow transplantation, and great strides

* *Corresponding author*
Email: eoppongbekoe@ug.edu.gh

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

have been made in its administration, though it still carries some risks of morbidity and mortality [6]. Hydroxyurea is widely used in orthodox medicine in the management of SCD. By downregulating the expression of ET-1 (endothelial) cells, hydroxyurea is recommended for recurrent and painful vaso-occlusive episodes. It also enhances clinical outcomes by increasing fetal haemoglobin [7]. Despite these positive outcomes, it has been established that hydroxyurea usage is associated with cytotoxicity and myelosuppression [8]. Other adverse effects include mild peripheral skin hyperpigmentation, cytopenias, elevation of hepatic enzymes, gastrointestinal symptoms, anorexia and infertility [9]. These side effects serve as barriers to medication adherence in especially children with SCD [10]. SCD is thus, a chronic illness with catastrophic psychological and clinical implications, prompting many affected patients to seek complementary and alternative medicine (CAM) [11].

The WHO recommends the integration of ethnomedicines into primary healthcare because about 70 to 95 percent of people, especially in developing countries, rely on them (WHO, 2013). Plants are crucial to the health of individuals and hence they have been used in the treatment of several diseases including jaundice, neurogenerative diseases and inflammation [12,13]. The discovery of the antisickling effects of some medicinal plants stemmed from efforts to develop alternative, less expensive, and less harmful treatments [14,15]. Several medicinal plants have been identified that are used in the folkloric management of SCD [16,17]. Therefore, there is a need to ascertain the efficacy of these medicinal plants. This review highlights the therapeutic interventions for SCD, with emphasis on the utilisation of herbal medicines, and a mini systematic review of two randomised controlled trials.

Epidemiology of sickle cell disease

SCD is prevalent in regions with historically high malaria incidence, such as sub-Saharan Africa, the Middle East, and portions of the Indian subcontinent [2]. The significant convergence in the historical prevalence of haemoglobin S, α-thalassemia, and β-thalassemia indicates that the rise in the prevalence of heterozygosity for these mutations in certain populations was a result of the protective effect against malaria mortality. In these places, 5% to 40% or more of the population are haemoglobin S carriers [2]. The geographical region in Africa from Senegal to Madagascar accounts for roughly 75 percent of the approximated 300,000 to 400,000 neonates born annually with sickle cell anaemia (SCA), mirroring the endemicity of malaria on the continent [18]. SCD represents the most prevalent global hemoglobinopathy, accounting for 275,000 of the 330,000 infants born worldwide with a major hemoglobinopathy [19]. According to Agun and Odame (2012), SCD-related mortality rates differ tremendously over the world. The second most prevalent kind of SCD, HbSC disease, is particularly prevalent in West Africa [20]. SCD is linked to a high rate of pediatric mortality in underdeveloped nations where the condition is prevalent. Children with severe hemoglobinopathies (including SCD) born in high-resource nations have higher survival rates and reduced death rates than children born in low-resource nations [19]. SCD is characterised by a plethora of clinical presentations and it is linked to comorbidities and a shorter life span [4]. Asare et al. (2018) states that though acute episodes of pain are the main clinical feature of SCD, the individual living with the disease may also experience recurrent infections, chronic end-organ destruction, and vaso-occlusive crises (VOCs), which can start as early as 4 to 6 months of age and can persist throughout life. The pain which may become chronic has a substantial impact on the quality of life and affects patients, their families and the healthcare professionals who are providing treatment. Such healthcare providers are known to experience frustration, compassion fatigue, and burnout.VOCs continue to be the primary cause of SCD-related hospitalisations and account for $1.1 billion in yearly healthcare expenses [21,22].

Clinical complications of sickle cell disease

Clinically, SCD may affect multiple organs and systems in the body and has haematological complications such as haemolysis, vaso-occlusion with its related crisis, organ damage and infections [1]. SCD is marked by premature red blood cell destruction, which results in chronic anaemia and small blood vessel occlusion. The occlusion causes terrible body pain and complications including stroke, chest infections, pulmonary hypertension, osteomyelitis, priapism, liver disease and proliferative retinopathy [1].

Current Challenges with the Management of Sickle Cell Disease

Genetic Interventions for SCD Management Bone Marrow Transplantation (BMT). Bone marrow transplantation (BMT), also known as hematopoietic stem cell transplantation (HSCT), is currently the only curative treatment for SCD [20,23]. However, several obstacles impede its widespread utilisation. Firstly, the requirement for a human lymphocyte antigen-identical family member as a donor poses a significant challenge due to the limited availability of suitable donors. Despite efforts to encourage bone marrow donation, the pool of potential donors remains insufficient to meet the demand. Consequently, identifying individuals with an adequate risk-to-benefit ratio for BMT becomes paramount, further complicating the process [24]. Moreover, BMT entails significant risks and complications. The procedure is complex, carrying inherent risks such as infection, graft failure, graft-versus-host disease (GVHD), and organ damage [25,26].

GVHD can lead to inflammation and potential organ dysfunction as transplanted cells attack the recipient's tissues [26]. Additionally, intensive preparation and conditioning regimens, including chemotherapy, are necessary to suppress the recipient's immune system and facilitate engraftment [27]. However, these regimens are associated with debilitating side effects such as nausea, vomiting, hair loss, and increased susceptibility to infections, thus imposing substantial physical and

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

psychological burden on patients [27]. Mouth sores have been reported as the single most debilitating side effect (42%), followed by nausea and vomiting (13%) in patients who have undergone BMT. In the study, many patients mentioned that mouth sores made it difficult or impossible to eat, swallow, drink, and talk. Sixty-six percent of patients hence reported receiving opioid analgesics, most frequently morphine, to relieve oral pain [28].

Furthermore, despite meticulous matching and preparation, there remains a risk of graft rejection, necessitating additional treatment and potentially a second transplant [25, 26]. The long-term follow-up and care required for patients post-BMT further contribute to the burden on healthcare systems and patients alike [29]. Additionally, the high cost and limited accessibility of BMT, particularly in regions with constrained healthcare resources, exacerbate disparities in access to care for individuals with SCD [29]. Moreover, uncertainties surrounding long-term outcomes, including the risk of late effects such as secondary cancers, infertility, and chronic health conditions, underscore the need for further research to elucidate the implications of BMT for SCD [30].

Gene Therapy. Gene therapy represents a cutting-edge approach aimed at correcting the genetic mutation responsible for SCD. Although still in the experimental phase, these treatments offer the potential to cure the disease [31]. Researchers are employing therapeutic *ex vivo* techniques by introducing corrective genetic material into a patient's hematopoietic stem cells [27]. Gene therapy and gene editing technologies are considered as better alternatives for SCD treatment as initial findings suggest that gene therapy may result in fewer treatment-related toxicities compared to hematopoietic stem cell transplantation (HSCT) [32]. In one study, hematopoietic cells were modified *ex vivo* using a lentiviral vector carrying a gene construct targeting BCL11A, which leads to increased production of gamma globulin. This treatment involves myeloablative therapy followed by reinfusion of modified hematopoietic cells. A proof-of-concept study revealed significant improvements, including the absence of irreversibly sickled cells in peripheral smear and reduced hemolysis in one patient. Further analysis showed that nearly a quarter of red blood cells carried fetal haemoglobin (HbF). The increase in HbF leads to reduced levels of sickle red blood cell which decreases the likelihood of red blood cell polymerisation [33].

Disease Modifying Treatments for SCD Management

Hydroxyurea. Considering the challenges associated with BMT, pharmacological interventions remain the mainstay of SCD management, especially in developing countries. Hydroxyurea (HU), an effective medication, has shown promise in reducing the frequency of painful episodes and complications associated with SCD [34]. It increases both the foetal haemoglobin (HbF) and haemoglobin levels. In most cases, it reduces the frequency of painful episodes by 50%. A long-term analysis conducted in adult patients who had received up to 9 years of treatment found that HU was associated with a significant (40%) reduction in mortality [35]. Treatment of patients with HU decreased acute chest syndrome and the requirement for blood transfusions in randomised adult patient trials [23,34]. Children have successfully used HU, according to reports.

A study conducted with HU in children reviewed that the rate of vaso-occlusive episodes was reduced from 2 in the 12 months before enrolment to 0 after 12 months of treatment, and the number of hospitalisations was reduced from 2 to 0 during the same time frame [35]. The evidence that hydroxyurea therapy benefits children and adults with homozygous SCD is overwhelming. Unfortunately, multiple barriers exist to its use in patients with SCD, and studies have found that adherence to hydroxyurea is often poor. HU has many side effects such as myelosuppression, skin reactions, fever, amenorrhea, bleeding, weight gain, as well as the need for frequent venipuncture which negatively impact initiation of and long-term adherence to treatment. Hydroxyurea is also potentially carcinogenic [36].

L-glutamine. In 2017, the US FDA approved the use of L-glutamine to mitigate acute complications of homozygous SCD in individuals aged five years and older [37]. L-glutamine is involved in a multifaceted, indirect mechanism that potentially decreases the vulnerability of sickle erythrocytes to oxidative harm. The approval of L-glutamine hinged on a clinical investigation involving 230 patients who were randomly assigned to receive either L-glutamine or a placebo; around 66% of participants in both cohorts were concurrently administered hydroxyurea. There was a lower incidence of pain crises in the individuals who were treated with L glutamine compared to the individuals who were given the placebo [37,38]. While there exists limited research delving into the significance of L-glutamine supplementation, further studies are imperative to ascertain its efficacy conclusively [37,39].

Crizanlizumab. Crizanlizumab is a humanised monoclonal antibody that binds to P-selectin, preventing its interaction with P-selectin glycoprotein ligand and inhibiting the adhesion of white blood cells (WBCs) and red blood cells (RBCs) to the vascular endothelium [39]. It has been studied both alone and in combination with hydroxyurea therapy for the prevention of sickle cell-related crises in patients with SCD [39]. In a double-blinded, randomised, placebo-controlled phase 2 trial, participants receiving concomitant hydroxyurea and those not receiving it were randomly assigned to receive crizanlizumab at doses of 2.5 mg/kg or 5.0 mg/kg, or placebo.

Among patients receiving high-dose crizanlizumab, the median rate of crises per year was 45.3% lower, dropping from 2.98 per year with placebo to 1.63 per year with crizanlizumab. High-dose crizanlizumab also significantly increased the median time to the first crisis to 4.07 months from 1.38 months ($p = 0.001$), as well as the median time to the second crisis (10.32 months versus 5.09 months). Notably, crisis rates were reduced both in patients receiving

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

hydroxyurea (32.1%) and those not receiving it (50.0%) [40]. Crizanlizumab represents a significant advancement in the treatment of SCD, offering patients a targeted therapy to manage the symptoms and complications associated with the disease. However, it is associated with side effects of infusion reactions, fever, nausea, joint pain, arthralgia, diarrhoea, pruritus, vomiting, and chest pain [21]. Crizanlizumab is currently inaccessible in most low-income countries [41].

Voxelotor. Voxelotor, a promising therapy for SCD, received accelerated approval from the US FDA on November 25, 2019 [42]. It targets HbS polymerisation by forming a reversible covalent bond with the N-terminal valine of the α chain of haemoglobin, leading to a conformational change that increases haemoglobin's affinity for oxygen, thus reducing the availability of deoxygenated HbS for polymerisation [20,39]. Preclinical studies have shown improved red blood cell (RBC) formation and increased blood viscosity *in vitro*. Clinical trials, including a phase 1/2 randomised, double-blind, placebo-controlled trial followed by a single-arm, open-label extension study, evaluated Voxelotor's efficacy in adults with SCD.

Treatment with Voxelotor at doses of 500, 700, or 1000 mg/day for 28 days, or 700 or 900 mg/day for 90 days, resulted in no sickle cell crises during treatment [43]. Furthermore, improvements in surrogate markers such as increased haemoglobin, reduced haemolysis, and a decline in the percentage of sickled red cells were observed [43,44]. One significant disadvantage of Voxelotor is the lack of extensive long-term data regarding its safety and efficacy. Patients with SCD often require lifelong treatment, making the absence of comprehensive long-term data a cause for concern. Without a thorough understanding of Voxelotor's long-term effects, including its impact on disease progression and potential adverse events, there is a risk of unforeseen adverse reactions or complications arising with continued use [43]. Data on the availability of Voxelotor in lower and middle income countries, including Ghana is scarce and even if it is available, the cost will be high enough to hinder access to this medication.

Long-Term Blood transfusion. Long-term blood transfusion has also been used to manage SCD. However, the disadvantage of employing long-term blood transfusion as a means of managing SCD is the risk of iron overload [45]. This is managed by iron chelation therapy, but long-term blood transfusion is stressful and costly [46]. There are also immune-related issues such as alloimmunization, where the immune system develops antibodies against transfused blood components, potentially complicating future transfusions. Furthermore, transfusions can lead to infectious risks despite modern screening methods, as well as non-infectious complications like transfusion-related acute lung injury and multiorgan system failure, particularly in patients with predisposing conditions. The complications highlight the importance of vigilant transfusion practices and emerging strategies to mitigate these risks.

Adjunct Therapy for The Management of SCD

Analgesics. The 2014 Expert Panel Report recommends a treatment protocol for SCD patients experiencing acute pain episodes, to start analgesics quickly, within 30 minutes of triage or 60 minutes of registering. For individuals with mild-to-moderate pain, nonsteroidal anti-inflammatory medications were recommended as were opioids prescription for those with severe pain.
Morphine, hydromorphone, fentanyl as well as other opiates have been studied as medicines used to manage SCD, especially in severe painful episodes [35]. However, the appropriateness of their use for the extended treatment of chronic non-cancer-related pain is a matter of contention for various reasons. One of the key reasons is the high phenomenon of psychological addiction that these drugs can produce. Even so, the extent of their efficacy in the management of chronic pain has not yet been conclusively demonstrated [47]. Side effects from these analgesics may include insomnia, asthenic conditions, and peripheral oedema, constipation, respiratory depression, and hormonal dysfunction [36].

Antibiotics. Penicillin is administered to children as prophylaxis because of the increased risk of life-threatening pneumococcal infections associated with the disease. In SCD, the spleen's immunological functions, including the removal of bacteria from the bloodstream and the production of antibodies, become progressively impaired, leading to an increased susceptibility to infections [19]. Hypersensitivity is the most significant adverse reaction to penicillin, and it can result in rashes, anaphylaxis, and even death [48]. One to 10 percent of those exposed to penicillin get allergic responses [36].

Medicinal plants used in the management of sickle cell disease

In resource-constrained regions where access to conventional healthcare is often limited, traditional herbal medicines have long been relied upon for managing various ailments, including SCD. The prevalence of SCD in these areas, combined with the challenges in accessing modern medical facilities, has led to the exploration of indigenous plant-based remedies as alternative treatment options [19]. Various ethnopharmacological studieints have documented plants that are traditionally used in the management of SCD [15-17]. One notable study highlighted the potential of three plant species-*Cajanus cajan* (pigeon pea), *Carica papaya* (papaya), and *Zanthoxylum zanthoxyloides* (West African black pepper), in managing SCD. These plants, rich in secondary metabolites such as tannins, alkaloids, saponins, flavonoids, and glycosides, exhibited significant antisickling properties *in vitro* [49]. This suggests their potential as alternatives to conventional medications.

Moreover, collaborations between researchers and traditional healers have highlighted the in-depth botanical knowledge ingrained in local communities. In the city of Kitty in the Democratic Republic of Congo, for instance,

traditional healers identified numerous plant species (*Curcuma longa*, *Fagara tessmannii* Engl, *Piptadeniastrum africanum* (Hook. F.) Brenan, *Persea americana* Mill, *Harungana madagascariensis* Lam. exPoir,) Pierre ex Heckel *Ficus thonningii* Blume, *Ricinodendron heudelotii* Baill., *Chrysanthellum americanum* (L.) Vatke, *Lannea kerstingii* Engl K. Krauss, *Jatropha curcas, Bridelia micrantha* (Hochst) Baill, and *Jatropha gossypiifolia* Linn.) with intriguing antisickling properties [16]. This collaborative effort not only validates traditional practices but also underscores the importance of preserving indigenous knowledge for healthcare purposes. Furthermore, in a study to investigate the antisickling activities of two ethnomedicinal recipes used in the management of SCD, the recipe that contained *Vernonia amygdalina* Dcl, *Garcinia cola* Heckel, *Mangifera indica* Linn., *Terminalia catappa* Linn. *Newbouldia laevis* Seem, Z. zanthoxyloides(Lam.) Waterm. and *Capsicum frutescens* Linn. was found to have good antisickling activity (15).

An ethnopharmacological survey conducted in western Cameroon further documented the diverse array of medicinal plants used in managing SCD. These plants (*Albizia ferruginea (Guill. et Piero) Benth*., *Treculia africana Decne*, *Ficus tremula Warb*., *Bougainvillea sp comm. ex Juss*, *Hymenocardia acida Tul*,*Gardenia leopoldiana De Wild & T. Durand*, *Morelia Senegalensis A. Rich. ex-DC*, *Stipularia africana P. Beauv*., *Sterculia bequaertii De Wild, Justicia secunda Vahl., Rungia grandis T. Ander, Alternanthera bettzickiana repens (L.) Link, Annona senegalensis Pers., Ceiba pentandra (L.) Gaertn., Carica papaya L., Alchornea cordifolia M¨ull. Arg., Vigna unguiculata (L.) Welp., Bridelia ferruginea Benth., Millettia laurentii De Wild, Hypoxis angustifolia Lam., Leocus africanus (Bak. ex. Elliot) J. K. Morton* and *Dissotis brazzae Cogn)*, sourced from various botanical families, are prepared using methods ranging from maceration to decoction. The phytochemical analysis of these medicinal plants has revealed a plethora of bioactive compounds, including alkaloids, terpenoids, saponins, flavonoids, anthraquinones, and polyphenolic compounds, which contribute to their therapeutic effects. The study further investigated the *in vitro* antisickling properties of these plants and showed that *Alchornea cordifolia M¨ull. Arg., Alternanthera bettzickiana repens (L.) Link, Annona senegalensis Pers., Dissotis brazzae Cogn., Hypoxis angustifolia Lam. Justicia secunda Vahl* and *Vigna unguiculata (L.) Welp* posses high antisickling properties [16].

Recent studies have also delved into the antisickling properties of specific plant-derived compounds. For example, divanilloylquinic acids which were isolated from *Fagara zanthoxyloides*; burkinabins A, B, C demonstrated antisickling activity comparable to sodium cromoglycate. This highlights the potential of isolating and synthesising bioactive compounds from medicinal plants for targeted therapeutic interventions [50]. In addition to these findings, historical evidence and traditional practices suggest the efficacy of various plant extracts, including *Pterocarpa osun, Piper guineensis, Eugenia caryophyllala,* and *Sorghum bicolor*, in managing SCD [51]. Table 1 summarises the available information on the phytoconstituents, antisickling properties (ethnomedicinal mention, *in vitro* and *in vivo* studies), effect on anaemia and toxicological data of the aforementioned plants. Plants such as *Fagara tessmannii* and *Hypoxis angustifolia* have limited information on their use in SCD. Most of the plants require robust clinical studies to determine their efficacy versus toxicity for use in SCD. The exploration of traditional herbal medicines for managing SCD offers a promising avenue for improving healthcare and treatment outcomes in SCD. Integrating indigenous botanical knowledge with modern scientific research can lead to the development of safe, effective, and culturally relevant treatment options for SCD.

Use of Complementary and Alternative Medicines (CAM) in SCD Management

An increasing number of patients have turned to CAM and naturopathic substances in the management of painful episodes associated with SCD [52]. Naturopathy is a holistic healing approach that integrates a variety of treatments and natural therapies, with the underlying concept that human body possesses an inherent capacity for self-healing when provided with adequate support. It represents a unique form of primary healthcare, encompassing the realms of art, science, philosophy, and the application of diagnosing, treating, and preventing illness [53]. Numerous techniques and methods can be used in naturopathic treatment, including dietary counselling, herbal medicines, hydrotherapy, iridology, massage, nutritional supplements, and osteopathy. The most prominent alternative medical practice outside of the allopathic medical system is naturopathy. Homoeopathy, nutritional therapy, ayurvedic medicine, yoga, and meditation are all acknowledged components of naturopathic treatment's holistic approach [53]. Homoeopathy involves treating symptoms with minute amounts of natural compounds that would ordinarily cause the same outcome if consumed in much higher proportions [54].

In a study to investigate integrative holistic therapies for children and adults with SCD, 85% of the participants employed non-conventional approaches in addition to treatments in the management of SCD, with 6% of them using homeopathy [55]. According to the study, 53% of participants employed massage therapy while 10% used vitamin therapy. Another study to ascertain the factors associated with the use of CAM revealed the following percentage usage among two hundred and twenty-seven participants; homeopathy - 1.1 %, massage - 14.4%, yoga and mega vitamins - 2.2% [52]. An increasingly crucial part of supportive therapy for patients with SCD is dietary care, particularly in regions with limited resources (56). Recently, focus has been given to nutritional studies in SCD due to particular dietary deficiencies and benefits brought on by fewer painful episodes [57]. Micro and macro nutrient deficiencies can play a role in worsening symptoms of SCD.

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

For instance, arginine plays a pivotal role in the pathophysiology of SCD, and hence insufficient or low arginine bioavailability is associated with SCD complications. Also, being a crucial ingredient for the functioning of metalloenzymes (such as ceruloplasmin) and playing a significant role in iron metabolism, copper deficiency is linked to anaemia [57].

Outcome Measures for SCD

Clinical outcome measures are parameters or tools used in healthcare to determine the effects of drugs, and interventions. For SCD these include pain, level of anaemia, and renal and hepatic effects among others. These measures are used evaluate the efficacy and safety of administered drugs in the patient.

Pain. Pain is a critical parameter for assessing treatment efficacy in sickle cell anemia, as it is the primary symptom driving patients to seek medical care [58]. Due to the subjective nature of pain perception, patients can provide input on the efficacy of medications in real-time. Thus, any reduction in pain severity or frequency signifies a positive response to the treatment. Additionally, effectively monitoring and reducing pain not only indicates a favorable response to treatment, but also greatly improves the quality of life for SCD patients [59].

Severity of Anaemia. In SCD, there is a genetic variation of human haemoglobin whereby a point mutation in the β globin gene causes valine to replace glutamic acid at the sixth position of the β globin chain. Monitoring haemoglobin levels is essential since low levels can indicate anaemia, which is common in such patients due to the shortened sickle cell lifespan and chronic hemolysis of red blood cells [60]. An effective sickle cell management strategy should aim to increase haemoglobin levels and reduce symptoms of fatigue, shortness of breath, and problems related to reduced oxygen-carrying capacity [61]. Apart from haemoglobin levels, packed cell volume (PCV) and the overall red blood cell status can be used to assess anaemia. A decreased PCV value signifies a low portion of red blood cells in the total blood volume and this is indicative of anaemia [62,63].

Renal and Hepatic Effects. Although hepatic enzymes may not directly indicate the effectiveness of treatment for SCD, it is nonetheless crucial to monitor liver function in such patients, more especially in patients undergoing therapies such as long-term transfusions, or drugs that may cause liver injury as this is because many medications have extremely reactive and hazardous intermediate products that form during metabolism [64]. Any variation from normal levels of liver enzymes requires careful study to determine whether the treatment regimen is unintentionally causing harm. By meticulous monitoring, medical personnel can make well-informed judgments that protect the health and safety of those receiving treatments for SCD [65]. Tests for liver and kidney function are also essential components of safety evaluations in herbal medicine clinical trials. Monitoring kidney and liver function aids in the early detection of toxic substances and metabolites and determines whether the substances pose a risk to participants [66].

MATERIALS AND METHODS

Search Strategy

On the 6th of July 2023, a search was conducted in PubMed, Scopus (Elsevier), CINAHL Plus, and the Cochrane Central databases to gather information regarding the effectiveness of naturopathy and herbal medicines in managing SCD. The search employed the following terms or keywords: Herbal medicine, Herbalism, Homeopathy, Naturopathy, SCD, controlled clinical trial, and randomised control trial (RCT).

Eligibility Criteria

This review included all randomised control trials that were conducted with people of all ages in any setting who had SCD and had their diagnosis confirmed by electrophoresis. Administration of naturopathy and medicinal plants by either oral, topical or parenteral route compared to a placebo was accepted. All published trials without limitation to the year of publication were included in the study.

Exclusion Criteria

Unpublished studies, non-English articles, and articles that were not randomised control trials were excluded. Pure compounds derived from plants were excluded.

Study Outcomes

The primary outcome measures of the study were the frequency, severity, or duration of painful crises. The secondary outcome measures were adverse events or side effects, severity of anaemia in participants and quality of life.

Study Selection

The retrieved literature were imported into Endnote 20 and duplicate records were removed. The next step involved the title and abstract screening where articles were eliminated based on whether their titles or abstracts were related to the subject matter. The full-text screening was performed next, where the articles were included based on the pre-specified inclusion criteria. Another reviewer conducted the screening process independently and discrepancies in results were resolved by a third reviewer.

Inclusion

All herbal medicines which included herbs, herbal materials and their formulations whose determination of efficacy were via randomised controlled trials.

Data Extraction

Data extracted from the RCTs included information on the study, study design, participant demographics, number of participants in intervention and control groups, interventions, herbal ingredients, and outcomes such as frequency and severity of painful crises and adverse effects.

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Risk of Bias Assessment

The risk of bias was assessed by RoB 2 (Revised Cochrane Risk-of-Bias tool for randomised trials), by considering several domains including the randomisation process, outcome measurement, missing outcome data, deviations from intended interventions, and selection of reported results. A final assessment of the study's overall risk of bias was determined after separately evaluating each domain [67]. Two individuals independently assessed the quality of each trial, and a third reviewer was consulted in the case of discrepancies. The risk of bias domains is illustrated through percentages across the two randomised control trials. A final judgement was also given in the risk assessment.

RESULTS AND DISCUSSION

The efficacy of a drug or medicinal plant is its ability to produce an effect. The efficacy of medicinal plants on SCD can be measured using indicators such as pain and level of anaemia. Pain is the primary symptom that prompts individuals to seek medical attention in sickle cell anemia [58]. Consequently, any decrease in the intensity or frequency of pain indicates a favourable reaction to the therapy. The majority of studies on the harmful effects of herbal remedies are linked to hepatotoxicity, whereas reports of other harmful consequences, such as renal impairment have also been recorded in medical literature [65].

Characteristics of studies

A total of two hundred five (205) articles were obtained from the searches, and after duplicate removal, the number of studies was reduced to one hundred and eighty-five (185). After screening the titles and abstracts, one hundred and eighty-two (182) were excluded. These articles were removed on the basis that they were not RCTs. Full-text screening was conducted for three (3) articles and one was excluded because it did not meet the eligibility criteria. For this reason, two (2) studies were selected for the review namely Wambebe et al., 2001 [51], and Akinsulie et al., 2005 [68].

Characteristics of participants

This systematic review involved two studies conducted by Wambebe et al. (2001) and Akinsulie et al. (2005). These studies included one hundred and fifty-seven patients with SCD; minimum and maximum age of the respondents were 1 year and 45 years respectively. All SCD diagnoses were confirmed by either electrophoresis, DNA analysis or high-performance liquid chromatography. Akinsulie et al. (2005) involved only children who were between 1 and 15 years whereas Wambebe et al. (2001) involved participants between the ages of 2 and 45 years. The latter study involved a double-blinded randomised control trial conducted for Twelve (12) months while Akinsulie et al. (2005) carried out a single-blinded placebo-controlled study conducted for a period of 6 months. Details of these studies are provided in Table 2.

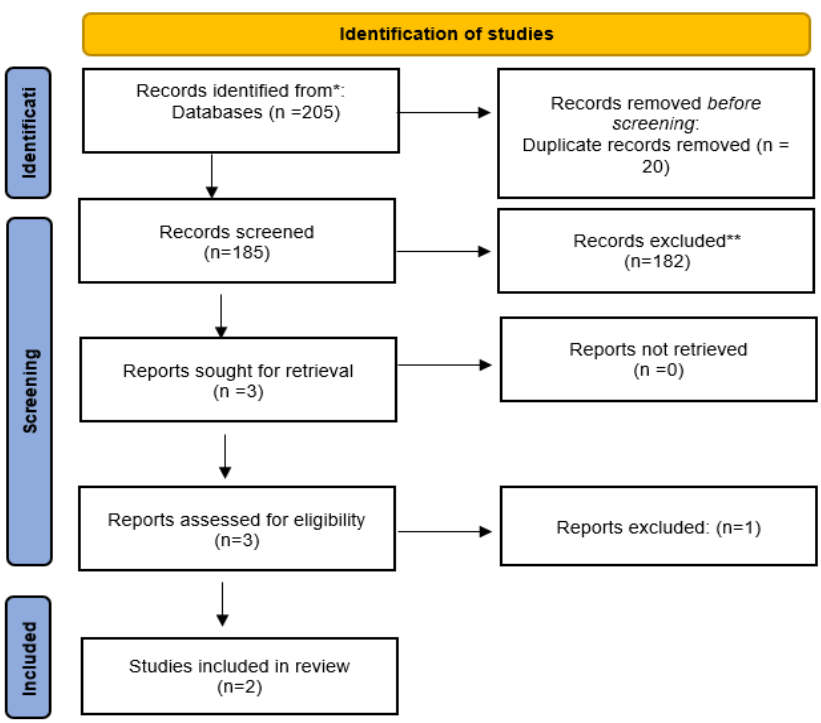

Figure 1. A PRISMA flow diagram of the systematic review study selection process

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Risk of Bias

With bias from intended interventions, both studies had some concerns. Considering bias due to missing outcome data, both studies had low risk. Although bias in the measurement of the outcome data was low risk for Wambebe et al. (2001), both studies had some concerns about the bias in the selection of the reported results because there was no pre-specified analysis plan that was used in executing the RCTs. Overall, while the studies may be quite dependable there may be some areas in which bias or possible need for improvement exist. These should be taken into consideration when interpreting or depending on the study's findings. Figure 2 below provides the risk of bias assessment for each article.

Intervention

The interventions assessed in the study consisted of two phytomedicines namely Niprisan® (a multiherbal standardised capsule from the freeze-dried extract of *Pterocarpus osun* stem, *Sorghum bicolor* leaves, *Eugenia caryophyllum* fruit and the lyophilised extract of *Piper guineenses* seeds) and Ciklavit® (a mono-herbal extract of *Cajanus cajan*). Niprisan was administered as a capsule in a dose of 12mg/kg in the study by Wambebe et al. (2001). On the other hand, Akinsulie et al., 2005 assessed the effectiveness of Ciklavit® an aqueous extract derived from the dried seeds of an edible bean, *Cajanus Cajan* (pigeon pea). The administration of Ciklavit® involved a liquid dosage, with children aged 5 years and below receiving 10 ml twice daily and 20 ml twice daily to those above 5 years.

Comparison

The comparison for both studies was a placebo. The placebo used in the Wambebe et al. (2001) study, had similar colour and aroma as the test drug [51]. For the Akinsule et al. (2005) study, the placebo contained 400 mg zinc, and 50 mg ascorbic acid [68].

Outcome

Outcomes considered by Wambebe et al. (2001) were severe and mild pain reduction, quality of life measured, anaemia and the effect of the phytomedicine on the liver and kidney [51]. The outcomes measured by Akinsulie et al., 2005 also included painful crises, effects of the medicine on the liver and kidney, hepatomegaly, and mean pack cell volume [68]. The primary symptom of SCD is pain, and the most common reason for hospital admissions is an intense painful crisis [69]. Effectively managing and reducing pain reflects a favourable response to treatment and greatly improves the quality of life for long-term illness [70]. Compared to patients receiving a placebo, patients using Niprisan® reported much fewer episodes of severe pain [51]. Niprisan® may therefore help prevent severe intravascular sickling of red blood cells. However, the study found no significant differences in the number of patients in both the test and control groups reporting mild to moderate pains. *In vitro* studies have outlined the antisickling properties of the constituents of Niprisan®; confirming the findings of the study [71-73]. In addition, according to Iyamu et al. (2002), Niprisan® was also found to have antisickling activity *in vitro*. In Akinsule et al., (2005) it was observed that the number of painful crises in the Ciklavit® group reduced from 207 to 191 but increased in control from 109 to 164 [68] suggesting that Ciklavit® may cause a reduction in the number of painful crises. This conforms with studies that show that *Cajanus Cajan* has anti-sickling properties *in vitro* [14,49]. Observations from the current study also agree with another study which showed that a combination of unrefined juice extracts from *Persia americana*, *Citrus sinensis*, *Carica papaya*, and Ciklavit® can inhibit sickling *in vitro*. Ciklavit® produced a sustained reduction in the number of sickle cells in both HbAS and HbSS blood samples [74]. Participants' quality of life was also evaluated using the health below average indicator, which was self-rated. In Wambebe et al. (2001) there was a significant difference in means concerning health below average after the washout period.

The study also showed improvement in work attendance by the study participants presumably due to improved quality of life from the successful management of SCD complications [51]. Anaemia is another relevant indicator when assessing the efficacy of drugs used to treat SCD. Low haemoglobin levels in sickle cell anaemia can cause fatigue, shortness of breath and issues related to decreased oxygen-carrying capacity. Effective treatment for sickle cell anaemia should aim to raise haemoglobin levels and reduce symptoms. In the Niprisan® study, there was an increase in haemoglobin level from 8.6 g/dl to 8.9 g/dl in the treatment group though not significant [51]. Akinsule et al., 2005 measured the packed cell volume in both test and control groups. In the test group, there was a decrease in the packed cell volume (PCV) in comparison with the PCV in the control group. However, the changes in both groups were not significant [68]. The results show that Ciklavit® may not be beneficial in improving anaemia in sickle cell patients whereas Niprisan® had no effect on anaemia status as there were no significant differences between the means either within or between groups.

Liver and kidney function tests are sensitive indicators of adverse effects caused by herbal products and other drugs. Abnormal liver enzyme levels may indicate liver injury or an alteration in bile flow [75]. The activity of liver enzymes was not significantly altered by Niprisan® and may thus suggest its non-involvement in acute liver damage. Another study found Niprisan® to be safe and non-toxic, agreeing with this study [76]. However, an extended period of research is necessary to provide a definitive conclusion, as sickle cell patients are likely to use these drugs over an extended duration. There were no significant differences between groups with regards to bilirubin, urea or creatinine levels according to Akinsulie et al. (2005) indicating that Ciklavit® may also not have negative effects on the liver or kidney. The findings of the study align with another study by Imaga et al. (2013) which also revealed no obvious changes in liver enzymes and urea and creatinine levels after Ciklavit® administration thus indicating no likely

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

harm to the liver and kidney. The findings of the study align with another study by Imaga et al. (2013) which also revealed no obvious changes in liver enzymes and urea and creatinine levels after Ciklavit® dministration. Hepatomegaly was seen in 55.3% of the cases at the start of the research and 33.3% at the conclusion in the group taking Ciklavit®. The placebo group experienced an increase in hepatomegaly from 42.9 per cent to 50 percent. This could indicate that Ciklavit® may have positive effects on liver liver health, and further studies are needed to ascertain this. Regarding adverse effects, clinicians observed no significant side effects during the Wambebe et al. (2001) study. The macular rashes observed in two patients taking Niprisan® could be regarded as a mild allergic reaction, as they spontaneously cleared within a few days without the need for treatment. For Akinsulie et al. (2005) side effects were transient and occurred in 8 percent of the participants (3 cases and 4 controls).

Table 1. Medicinal Plants used in the management of SCD

Plant	Phytoconstituents	Antisickling properties	Ameliorating pain	Improving anaemia	Toxicity
Bridelia micrantha (family Phyllanthaceae)	Phenolics, tannins, saponins, alkaloids, flavonoids, and glycosides [77].	This was among 44 plants used by herbalists and judged to be efficacious in SCD management [78].	*Bridelia* species contain various flavonoids which may justify their ethnomedicinal use for pains in African and Asian traditional medicines [79].	Extract caused non-significant increases in the values of RBC count, PCV and hemoglobin at 125 and 250 mg/kg [80,81]	Oral administration of the methanolic bark extract and a the fraction F6 800 mg/kg for 28 days did not induce toxicological damage in rats [82].
Harungana Madagascariensis (family Hypericaceae)	Alkaloids, phenolic compounds, saponosides, sterols, polyterpenes [83].	A recipe of three plants: *Zanthoxylum leprieurii, Xylopia aethiopica* and *H. madagascariensis* showed strong antisickling activity by Emmel's method [83].	Analgesic effects of the stem-bark ethanolic extract in mice and rats have been established [84].	Oral administration of ethanol leaf extract had anti-anaemic potentials [85].	Use of the ethanol fruit extract is cautioned with especially prolonged usage as it had nephrotoxic and hepatotoxic potentials, especially when consumed at high doses (≥ 1.25 g/kg) [86].
Fagara tessmannii (family Rutaceae)	Alkaloids, terpenoids, saponins, mucilage, coumarin, phenols compound including flavonoids, tannin (gallic tannin, phlobatannin) [87].	NR	It is used in traditional medicine for the treatment of tumors, swellings, inflammation [87]	NR	NR
Ficus thonningii Blume (family Moraceae)	Alkaloids, tannins, saponins, volatile oils, phenols and flavonoids in the fruit, leaves, stem, and root barks [88,89].	It has been used in traditional medicine for SCD, and has the capacity to reduce oxidative stress and infections that are rampant in such patients [90]	The methanol leaf extracts showed anti-inflammatory activity at 57.5% compared to acetylsalicylic acid 93.2% [89].	An extract of *Ficus thonningii* may improve red blood cell and PCV levels [91].	With subacute dosing with hydroethanolic extract, biochemical analysis revealed a slight elevation of liver parameters with 500mg/kg, while no significant increase was observed for kidney parameters [92]. Acute oral toxicity of methanol leaf extract showed an LD50> 5g/Kg [89, 93]
Chrysanthellum americanum (family Compositae)	Leaves contained flavonoids, saponins and tannins [94].	NR	NR	NR	Aqueous extract can be considered safe in oral administration at the dose tested since it did not causing no lethality or undesirable effects [95].

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 1. Cont.

Plant	Phytoconstituents	Antisickling properties	Ameliorating pain	Improving anaemia	Toxicity
Curcuma longa (family Zingiberaceae)	Curcuminoids, curcumin, essential oils (turmerone, zingiberene), polysaccharides, tannins, phenolic compounds, flavonoids [96].	The total methanolic extracts of the rhizome, leaves, roots and floral parts (petals and sepals) investigated in the Emmel test showed a high antisickling activity [97].	Its component, curcumin, has shown promise in reducing pain in various conditions [98,99].	Some curcumin feeding animal trials have not reported adverse effects on iron status, while others state that long time curcumin supplementation can aggravate iron deficiency leading to anemia [100]. In another study curcumin caused decrease in red blood cells resulting in anaemia. Curcumin binds to ferrous iron making it unavailable for hemoglobin [101].	Turmeric and curcumin are nontoxic when orally ingested by humans [102], however high doses or prolonged use may lead to gastrointestinal issues and toxicity in the liver, including nausea and diarrhea [103].
Persea americana (family Lauraceae)	Saponins, phenolic, carotenoids, compounds, glutathione, monounsaturated fats primarily oleic acid, vitamins, phytosterols [104]	Crude flavonoids from this plant displayed time- and dose-dependent anti-sickling activity [105].	This plant is reported to have anti-inflammatory properties and analgesic properties [106,107].	The ethanolic stem bark extract improved the red cell series and may be useful in treatment of anaemia because of its ability to cause a significant increase in PCV, RBC and Hb concentration [108].	No genotoxic effects were reported with the fruit pulp oil in *in vitro* or *in vivo* test systems. However, the highest dose led to an increase in aspartate aminotransferase, indicating hepatic or tissue damage [109].
Ricinodendron heudelotii (family Euphorbiaceae)	Tannins, terpenoids, glycosides, and alkaloids [110].	The aqueous extract reversed the shape of erythrocytes to normal, indicating antisickling activity [111].	Shown to have anti-nociceptive effects [112].	Traditionally used in anaemia treatment [113].	This plant is reported to not induce significant toxic effect below 3600 mg/kg bw [114].
Vernonia amygdalina (family Compositae)	The leaves contain saponins, alkaloids, flavonoids, tannins, ascorbic acids, beta-carotene, and reducing sugars [115].	Methanolic extract demonstrated high potency in maintaining erythrocyte membrane integrity and altering the polymerization of sickle cell hemoglobin at increasing concentrations [116].	Caused symptomatic relief of pain in malaria and in other pain and inflammatory conditions [117].	The leaves caused increase in white blood cell parameters, however, its continuous consumption might increase the risk of anaemia especially in menstruating and pregnant women [118].	The toxicity of the aqueous extract is greater than 5000mg/kg BW [119].

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 1. cont.

Plant	Phytoconstituents	Antisickling properties	Ameliorating pain	Improving anaemia	Toxicity
Jatropha gossypiifolia (family Euphorbiaceae)	Tannins, flavonoids, anthocyanins, alkaloids, triterpenes reducing compounds, steroids and mucilages, catechic tannins, sterols and terpenes [120,121].	This plant has antisickling and hemoglobin polymerization properties [120]. Part of a total of 117 plant species with anti-sickling activities [122].	In acidic corrosive initiated squirming test in mice, the methanol leaf extract was exceptionally significant in pain relief. (Pande et al., 2021). The latex of the plant also possesses anti-inflammatory and anti-arthritic activity which is attributed to its rich flavonoids content [123].	Widely used by people to treat anaemia in the Djougou area in northern Benin. In rats, it corrects anaemia within two weeks by stimulating the synthesis of hemoglobin and production and early release of immature red blood cells into the bloodstream [113].	The aqueous leaf extract is toxic, causing generalized loss of body weight, weakness, dizziness, appetite loss and restlessness in the acute toxicity studies. It altered profoundly the liver and kidney architecture [124].
Lannea kerstingii (family Anacardiaceae)	Steroids and triterpenes reported in the petroleum ether extract, steroid, triterpene, flavonoids and tannins in both crude methanol extract and chloroform fraction while the ethyl acetate fraction contained only flavonoids and tannins [125].	Traditionally used in sickle cell patients and pregnant women in Lomé [126].	NR	The aqueous leaf extracts had haematopoietic properties thus, justifying the use of the plant to alleviate anaemia in Togo. Stembark extract significantly corrected the anaemia induced by phenylhydrazine [127].	This plant causes significant inhibitory effect on ileum contraction, thus avoidance in cases of constipation is recommend [128]. The hydroalcohol extract showed teratogenicity in pregnant female rats [129].
Piptadeniastrum africanum (family Leguminosae)	Alkaloids, saponins, flavonoids, glycosides, phytate, tannins, oxalate and phenols, with high concentrations ofsaponins, terpenes and tannins [130].	Used in the treatment of SCD in the West Region of Cameroon [17].	Crude extract is associated with significant anti-inflammatory activity [113].	It showed positive results for pain comparable to aspirin (131), as well as antioxidant and pro-oxidant properties [132].	Reported hepatocellular and colonic damage [133], the liver of fishes also showed focal necrosis, bile stagnation, nuclear degeneration, hepatocytes with irregular shaped nucleus, cytoplasmic vacuolation, vascular congestion, bile pigment disintegration and cytoplasic degeneration, hyperplasia of epithelial cells and fusion of secondary lamellae [134].
Alchornea cordifolia (family Euphorbiaceae)	It is used traditionally in Africa to treat sickle cell anaemia. The leaves and its sub-fractions showed >70% suppression of HbSS erythrocyte sickling. Purified quercitrin also inhibited the polymerisation of isolated HbS and stabilized sickle erythrocytes membranes [135].	95 compounds including fatty acids, terpenoids, flavonoids, phenolic acids, alkaloids [136].	It is a phytotherapeutic agent in the management of painful disorders [137].	Treatment with the leaf extract in phenyl hydrazine induced anaemia enhances anti-anaemic properties [138].	liver sections of mice treated with 2000 mg/kg extract showed perivascular aggregates of lymphocytes, eosinophilia and pyknosis, evidence of hepatic damage [139].

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 1. Cont.

Plant	Phytoconstituents	Antisickling properties	Ameliorating pain	Improving anaemia	Toxicity
Alternanthera bettzickiana (family Amaranthaceae)	Extract showed the presence of saponins, tannins, terpenoids, flavonoids and glycosides [140].	Crude extracts of this plant showed good correction of sickling in red blood cells [141].	Results suggested that *A. bettzickiana* possessed antiarthritic potential, supporting its folkloric use for treating rheumatoid arthritis and pain [142].	NR	Sub-acute toxicity studies showed that up to 2000 mg/kg bw throughout 14 days of treatment, produced no toxic symptoms [143].
Annona senegalensis (family Annonaceae)	Polyphenols, flavonoids and tannins [144].	Plant extracts, anthocyanin crude extracts and the separated fractions possess a high antisickling activity [145,146].	Analgesic and anti-inflammatory effect of the methanolic extract is taught to be via peripheral mechanisms, thus justifying its folkloric use in the treatment of rheumatic pain [147].	Increased hematological parameters in treated albino rats, thus, the plant has a good immune boosting and treatment of anaemia potentials [148].	The root bark extracts are safe at the lower doses tested, but there are calls for caution in use at higher doses [149].
Bougainvillea sp (Family Moraceae)	Flower extracts revealed the presence of alkaloids, flavonoides, phlobatannins and terpenoids [150].	In *in-vivo* studies, anthcyanin extracts of the plant showed antisickling activity [151]	Traditional Mexican Medicine highlight its potential for the development of new treatments for pain and inflammation [152].	There was a significant reduction in packed cell volume, haemoglobin concentration and red blood cells at the dose 200mg/kg as compared to controls in *Bougainvillea spectabilis* leaves [153].	Water extracts derived from the pink, purple, and dark pink bracts of *B. glabra* have mild toxicity toward embryo [154].
Bridelia ferruginea (family Phyllanthaceae)	Rich in flavonoids, phenolics, phytosterols, triterpenes, saponins, alkaloids and cardiac glycosides [155].	Antisickling properties seen in *in vitro* studies, thus confirming its use by traditional healers in Congo for SCD [156].	At 25 to 100 mg/kg, i.p, both doses produced significant analgesic and antipyretic effects [157].	The leaf extract of plant is capable of stimulating blood cell formation. Haemological assay showed that B. ferruginea exhibited significant increase in packed cell volume, total hemoglobin, leukocyte, neutrophil and lymphocyte [158].	Root bark extract at 250, 500, and 1000mg/kg for 28 consecutive days in Wistar rats did not produce mortality and no significant differences were found in relative organ weights, and biochemical parameters studied [159].
Capsicum frutescens (Family Solanaceae)	Alkaloids, saponins, tannins, phlobatannins, flavonoids, combined anthraquinones, free anthraquinones and cardiac glycosides [160].	NR	The experimental evidence obtained in this laboratory animal study indicates that *C. frutescens* ethyl acetate extract (CFE) and capsaicin (CPF) have comparable anti-inflammatory effects to diclofenac [161].	A mixture of *C. frutescens* and *C. colocynthis* caused anaemia (reduction in red blood cells) accompanied by other adverse conditions [162].	A mixture of *C. frutescens* and *C. colocynthis* caused pronounced effects and death of rats. Vital organ lesions accompanied by anaemia and leucopenia were correlated with changes in serum ALP, AST and ALT activities with alterations in concentrations of total protein, albumin, urea and other serum constituents [163].

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 1. Cont.

Plant	Phytoconstituents	Antisickling properties	Ameliorating pain	Improving anaemia	Toxicity
Carica papaya (family Caricaceae)	Whole plant contains lycopene, carotenoids, alkaloids, monoterpenoids, flavonoids, mineral, vitamins enzyme papain [164], as well as folic acid, vitamin B12, saponins, glycosides, tannins and anthraquinones [165].	Phenylalanine, tyrosine and glycine reported in the unripe fruits of *Carica papaya,* are possible antisickling components and are responsible for their antisickling activity [166].	Leaves extract at 0.70 mg/kg bw showed the best analgetic activity that was comparable to aspirin [167].	It is a safe anti-anaemic drug candidate [168], while consuming papaya has a significant effect on changes in hemoglobin and hematocrit levels [169].	Single oral dose of the leaf extract is reported to cause significant changes in body weight, food and water consumption, but the weights of the internal organs were normal with. However, hemoglobin, hematocrit, red blood cell and total protein were significantly increased indicating dehydration [170].
Dissotis brazzae (family Melastomataceae)	Flavonoids, tannins, saponins, and other phenolics [171].	Anthocyanins extracted from the leaves displayed a significant antisickling activity, and decreased the Fe^{3+}/Fe^{2+} ratio in sickle red blood cells, and showed a radical scavenging activity with an IC50 of 43µg/mL [172].	NR	Extracted anthocyanins increased the hydration ability of red blood cells, which may improve anaemic conditions [141].	Ethanol extracts of Dissotis brazzae and Stomboisia schefflera had LC50 values >1000ug/ml indicating low toxicity in brine shrimp larvae [173].
Garcinia kola (family Clusiaceae)	Higher percentage of flavonoid, steroid, anthocyanin, saponins, tannins, combined and free anthraquinones, and phytate [174,175].	Methanol extract of the seed pod did not differ significantly from positive control in *in vitro* antisickling studies [156,175].	Clinically significant analgesic and anti-inflammatory effects in knee osteoarthritis patients [176].	In rats, an extract of *G. kola* raised the immune system while lowering RBC production, causing anaemia and having a negligible effect on PCV and HGB [177].	No effect on kidney function. Daily consumption reduces total cholesterol, the results on the liver function test showed that there was a significant ($p < 0.05$) increase in the AST and ALT levels [174].
Hymenocardia acida (Family Hymenocardiaceae)	Carbohydrates, tannins, flavonoids, saponins, alkaloids, cardiac glycosides, resins, steroids and terpenes [178].	An ethnomedicinal plant for SCD management in Nigeria [179]. The stem bark and leaves reversed the sickling of red blood cells in a dose-dependent manner [178,180].	It is used traditionally in Northern Nigeria for the management of different types of pain [181,182].	Very significant increase in red blood cell count with administration of the ethanolic root bark extracts [179].	Ethanolic root bark extracts are well tolerated on oral administration, even up to 6,000 mg/kg body weight. Chronic administration had observable organ damage at higher doses, with a focal area of hepatic necrosis, globule cells of the intestine were covered with progressive mucin and lymphocyte proliferations were observed within the spleen [179]. Other studies have also reported toxicities of this plant [181].

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 1. Cont.

Plant	Phytoconstituents	Antisickling properties	Ameliorating pain	Improving anaemia	Toxicity
Hypoxis angustifolia (family Hypoxidaceae).	Species of thIS genus are known to contain phenolic glycoside [183]	Extract and anthocyanin extracts showed antisickling effect [184,185].	NR	NR	NR
Newbouldia laevis (family Bignoniaceae)	Flavonoids, tannins, terpenes, steroidal and cardiac glycosides [186].	In *in vitro* studies, roots and stem barks of extracts had an anti-sickling activity [187,188]	The leaf and root extracts of the plant possessed dose-dependent analgesic, anti-inflammatory and anti-convulsant activities in rats [189], acting through a central and peripheral analgesic properties [190].	At 28 days, significant increase in percentage PCV, RBC counts, and haemoglobin values were noted [191]. There are also reports of possible anaemia with low doses (192).	Though the hydroethanol leaf extract is quite safe, it could cause anaemia at lower doses, infertility (both sexes), liver and kidney injuries at high doses [192].
Terminalia catappa (family Combretaceae)	Tannins, flavonoids, phenolic acids, triterpenes, triterpenoidal glycosides, lignan and lignan derivatives [193].	*In vitro* studies showed that fruits and leaves were agents for SCD therapy, and at 1mg/mL, solution of the extract was effective in preventing and reversing the sickling of human 'SS' erythrocytes [193].	Leaf extract significantly reduced the pain in the early phase formalin pain test [193].	Aqueous extract simultaneously interfere with the osmoregulatory and hemopoietic system of the blood and may be a panacea to anaemia [194]. The extract is also an erythropoietic agent that supports normal erythroid differentiation *in vivo* in phenylhydrazine-induced anemic mice [195].	The aqueous extract is reported not to have significant toxicity [196].
Treculia africana (family Moraceae)	Flavonoid, alkaloids, polyphenols, anthraquinones, saponins, oxalate, phytate, and cardiac and anthraquinone glycosides [197,198]	Ethnomedicinal use in the Democratic Republic of Congo [199]	A lectin from component possesses antinociceptive and anti-inflammatory properties [200]	Plant extract is capable of stimulating ref blood cell formation (erythropoiesis) and may be useful for haemopoietic conditions [201].	No toxicity recorded in cat fish models [202]. However a lectin component was shown to have hemagglutinating activity on human erythrocytes [203].
Vigna unguiculata (family Leguminosae)	Alkaloids, phenols, flavonoids and phytic acid (204).	Ethanol seed extracts showed good antisickling properties, which was dose dependent (205), and the anthocyanins extracts were found to be responsible for the sickling inhibition (206, 207).190	Potential analgesic activity, establishing the folkloric use of the plant in managing pain [208].	High contents of iron and zinc found in raw and cooked plant material which resolves anaemia resulting from iron deficiency [209].	Aqueous-Methanol pod extract had LD50 >5000 mg/kg in rat model, and oral administration for 28 days did not produce significant changes in biochemical and haematological indices. However, there was mild widening of the Bowman's capsule of animals administered with 1200 mg/kg and 1600 mg/kg [210].

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 2. Characteristics of the Included Studies

Study	Study Design	Study Participants	Period of Study	Diagnostic Criteria	Herbal Intervention	Control	ROA/ Dose	Routine Medications
Wambebe et al., 2001	Placebo-controlled double-blind cross-over trial Phase IIB (PIVOT)	70 Age: 2 to 45 years Individuals who suffered from moderate-to-severe recurrent episodes and had at least three painful or vaso-occlusive crises in the preceding year.	12 months	Hb electrophores is in alkaline or acid medium	NIPRISAN® *Pterocarpus osun* stem, *Eugenia caryophyllum* fruit and *Sorghum bicolor* leaves, the freeze-dried extract of *Piper guineenses* seeds,	Placebo	Oral 12mg/kg once daily	Folic acid, malaria prophylaxis and paracetamol
Akinsulie et al., 2005	Single-blinded placebo-controlled study	87 Age: 1-15 years Patients who did not have crises or evidence of organ failure	6 months	cellulose acetate paper electrophores is	Ciklavit® *Cajanus cajan*	Placebo	Oral Above 5 years and above: 20 mL twice daily 5 years and below: 10 mL twice daily,	Folic acid, proguanil or pyrimethamine

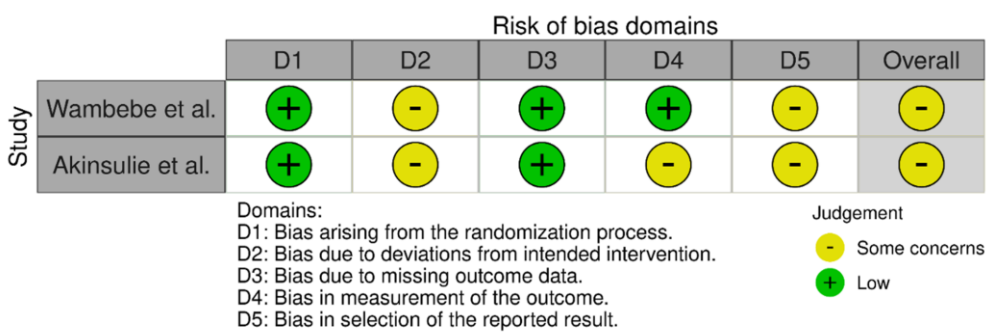

Figure 2. Risk of bias assessment for each article; Illustrating the judgement for the various domains and overall judgement.

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

Table 3. Efficacy and safety of herbal products

Study	Painful Crisis	Level of Anaemia	Quality of Life Measured	Hepatic and Renal Toxicity	Adverse Events
Wambebe et al., 2001	Mean mild to moderate pain 9.1 (Niprisan® group) to 20.6 (Placebo group), however this was not statistically significant. Following cross-over in the later half of the year, Group A (control) increased to 22.9 and Group B (Niprisan®) decreased to 6.2. There was no statistically noteworthy difference between the means. Mean severe pain: Group A (Niprisan®) was 7.9 compared to 22.1 in Group B (control). The result was statistically significant 6 months after crossover Group A (placebo) was 6.7 and Group B (Niprisan®) was 4.1. There was a statistically noteworthy distinction between the means	Non-significant change in anaemia level of 8.6 to 8.9 g/dL in the group on Niprisan®, and from 8.9g/dl to 9.2g/dL in the control group.	Absenteeism from work associated with SCD was reduced significantly in the Niprisan® group in the second six months of the study.	There is no significant difference between Gamma-glutamyl transferase levels and alkaline phosphatase levels in the placebo and intervention. Creatinine and BUN for renal function remained within the normal range and exhibited minimal variation. AST, ALT, levels alkaline phosphatase and GGT levels did not change significantly. This infers that Niprisan® did not cause acute liver and kidney damage.	Six participants experienced headaches while using Niprisan®, in contrast to two individuals on the placebo. Two patients had macular rashes for 3 days after commencing which resolved after 2 to 5 days.
Akinsulie et al., 2005	Number of painful crises in the Ciklavit® group reduced from 207 to 191 but increased in control from 109 to 164. Hepatomegaly on enrolment reduced from 55.3% to 33.3% at 6 months	Pack Cell Volume (PCV) The mean PCV at the beginning of the study, at 3 and 6 months was reduced in the test group and were 22.23% (4.14), 22.9% (3.61) and 21.24 % (3.43) respectively. The PCV in the control group had a notable increase. At the beginning, 3 and 6 months the values were 21.78% (3.37), 24.42% (5.30) and 22.78% (4.20)	Not reported	There were no distinctions in the number of children exhibiting clinical jaundice and in the average serum bilirubin throughout the entire study duration.	Tiredness and abdominal in 1 patient in the Ciklavit® Group. Peri-orbital swelling, diarrhoea, and itching eyes in control. Vomiting in 1 participant each from both groups.

Limitations of this review

Though the two reviewed studies reported promising results of the use of medicinal plants in the management of SCD, there were some weaknesses in the studies that included small sample sizes for both studies. Small sample sizes for such studies limit statistical power and generalizability of findings compromising the internal and external validity of the study. Also, random chance variations may also have a great impact on results. Although studies reported that participants were randomly allocated, the method of randomisation was not clearly stated. Intention-to-treat analysis was not stated, making it difficult to assess the validity of the evidence reported. Outcome measures among the studies varied, thus making direct comparisons and meta-analysis impossible.

Conclusion

This review assessed the efficacy and safety of two phytomedicines, Niprisan® and Ciklavit®, which have shown potential benefits in reducing painful crises associated with SCD. It further highlights their potential as complementary treatments for SCD management. Current

treatment challenges as well as potential herbal plants for sickle cell treatment have also been reviewed for their anti-sickling activity, and ability to reduce pain, ability to influence anaemia and possible toxic effects. Niprisan® in addition to its substantial reduction in the number of severe pain episodes also showed no effect on hepatic and renal functions, indicating no acute organ damage during the study period. Ciklavit® also showed a reduction in painful crises and seemed to have a positive impact on liver health, potentially alleviating the effects of sickle cell crises on hepatic function. Both interventions were generally well-tolerated, with mild side effects such as macular rash and headaches being reported in some cases.

The integration of herbal remedies in SCD management offers a promising pathway. These natural alternatives may serve as adjunctive therapies, helping to mitigate the painful episodes that characterise SCD thus improving patients' quality of life. However, standardised protocols for their use, as well as more rigorous clinical evaluations, are necessary to ensure their safe and effective integration into routine care.

DECLARATIONS

Ethical consideration
This manuscript does not contain direct studies involving animals or humans.

Consent to publish
All authors agreed on the content of the final paper.

Funding
None

Competing Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions
The literature search was done by SA and NA-S. Data extraction and analysis were performed by ERP and EAP. EOB conceptualised and supervised the study. All authors contributed to the drafting and approval of the final manuscript.

Acknowledgement
The authors would like to acknowledge the University of Ghana Library System for their assistance during the data search.

Availability of data
Data is available upon request to the corresponding author.

REFERENCES

1. Makani J, Ofori-Acquah SF, Nnodu O, Wonkam A, Ohene-Frempong K (2013) Sickle Cell Disease: New Opportunities and Challenges in Africa. Sci World J 2013
2. Saraf SL, Molokie RE, Nouraie M, Sable CA, Luchtman-Jones L, Ensing GJ, et al.. (2014) Differences in the Clinical and Genotypic Presentation of Sickle Cell Disease Around the World. Pediatr Respir Rev 15:4-12.
3. Rees DC, Brousse VAM, Brewin JN (2022) Determinants of Severity in Sickle Cell Disease. BMC Complement Med Ther 56:100983.
4. Oniyangi O, Cohall DH (2020) Phytomedicines (Medicines Derived from Plants) for Sickle Cell Disease. Cochrane Database Syst Rev
5. Rai P, Ataga KI (2020) Drug Therapies for the Management of Sickle Cell Disease. F1000Research 9: F1000 Faculty Rev-592.
6. Bolaños-Meade J, Brodsky R (2009) Blood and Marrow Transplantation for Sickle Cell Disease: Overcoming Barriers to Success. Curr Opin Oncol 21:158.
7. Sanyaolu A, Agiri E, Bertram C, Brookes L, Choudhury J, Datt D, et al.. (2020) Current Modalities of Sickle Cell Disease Management. Blood Sci 2:109-16.
8. Santos JL, Bosquesi PL, Almeida AE, Chin CM, Varanda EA (2011) Mutagenic and Genotoxic Effect of Hydroxyurea. Int J Biomed Sci 7:263.
9. Agrawal R, Patel R, Shah V, Nainiwal L, Trivedi B (2014) Hydroxyurea in Sickle Cell Disease: Drug Review. Indian J Hematol Blood Transfus 30:91-6.
10. Modi AC, Crosby LE, Guilfoyle SM, Lemanek KL, Witherspoon D, Mitchell MJ (2009) Barriers to Treatment Adherence for Pediatric Patients with Sickle Cell Disease and Their Families. Child Health Care 38:107-22.
11. Busari AA, Mufutau MA (2017) High Prevalence of Complementary and Alternative Medicine Use Among Patients with Sickle Cell Disease in a Tertiary Hospital in Lagos, South West, Nigeria. BMC Complement Altern Med 17:1-8.
12. Raghuvanshi D, Dhalaria R, Sharma A, Kumar D, Kumar H, Valis M, et al.. (2021) Ethnomedicinal Plants Traditionally Used for the Treatment of Jaundice in Himachal Pradesh in Western Himalaya- a Review. Plants 10:232.
13. Ilondu EM, Enwa FO (2013) Commonly Used Medicinal Plants in the Management of Sickle Cell Anaemia and Diabetes Mellitus by the Local People of Edo State, Nigeria. Int J Pharm Chem Sci 2:14-9.
14. Imaga NA, Chukwu CE, Blankson A, Gbenle GO (2013) Biochemical Assessment of Ciklavit®, a Nutraceutical Used in Sickle Cell Anaemia Management. J Herb Med 3:137-48.
15. Egunyomi A, Moody JO, Eletu OM (2009) Antisickling Activities of Two Ethnomedicinal Plant Recipes Used for the Management of Sickle Cell Anaemia in Ibadan, Nigeria. Afr J Biotechnol 8:020-5.
16. Kitadi JM, Mazasa PP, Sha-Tshibey Tshibangu D, Kasali FM, Tshilanda DD, Ngbolua K-T-N, Mpiana PT (2020) Ethnopharmacological Survey and Antisickling Activity of Plants Used in the Management of Sickle Cell Disease in Kikwit City, DR Congo. Evid Based Complement Alternat Med 2020:1-10.
17. NL Y, PCl BN, CA P, KD T, Fotsing CB K, PJ NN, et al.. (2022) Ethnopharmacological Study of the Medicinal Plants Used in the Treatment of Sickle Cell Anemia in the

West Region of Cameroon. Evid Based Complement Alternat Med 2022:5098428.

18. Oron AP, Chao DL, Ezeanolue EE, Ezenwa LN, Piel FB, Ojogun OT, et al.. (2020) Caring for Africa's Sickle Cell Children: Will We Rise to the Challenge? BMC Med 18:1-8.
19. Mulumba LL, Wilson L (2015) Sickle Cell Disease Among Children in Africa: An Integrative Literature Review and Global Recommendations. Int J Afr Nurs Sci 3:56-64.
20. Kato GJ, Piel FB, Rei CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al.. (2018) Sickle Cell Disease. Nat Rev Dis Primers 4.
21. Mahmood LA, Thaniel L, Martin B, Marguiles S, Reece-Stremtan S, Idiokitas R, et al.. (2021) Integrative Holistic Approaches for Children, Adolescents, and Young Adults with Sickle Cell Disease: A Single Center Experience. Complement Ther Med 60:102680.
22. Asare EV, Wilson I, Benneh-Akwasi Kuma AA, Dei-Adomakoh Y, SeY F, Olayemi E (2018) Burden of Sickle Cell Disease in Ghana: The Korle-Bu Experience. Adv Hematol 2018:6161270.
23. Kapoor S, Little JA, Pecker LH (2018) Advances in the Treatment of Sickle Cell Disease. Mayo Clin Proc 93:1810-24.
24. Kassim AA, Walters MC, Eapen M, Ritzau N, Smith M, Solh MM, et al.. (2023) Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe Sickle Cell Disease: BMT CTN 1507. Blood 142: LBA-4-LBA-.
25. Kassim AA, Wilkerson K, de la Fuente J, Seber A, Gouveia RV, Bonfim C, et al.. (2022) Outcomes of Non-Myeloablative HLA-Haploidentical Bone Marrow Transplant with Thiotepa and Post-Transplant Cyclophosphamide in Children and Adults with Sickle Cell Disease, a Phase II Trial: Vanderbilt Global Haploidentical Transplant Learning Collaborative (VGC2). Blood Rev 140:2383-5.
26. Walters MC, De Castro LM, Sullivan KM, Krishnamurti L, Kamani N, Bredeson C, et al.. (2016) Indications and Results of HLA-Identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease. Biol Blood Marrow Transplant 22:207-11.
27. Zulu S, Kenyon M (2018) Principles of Conditioning Therapy and Cell Infusion. Springer Int Publ 89-96.
28. Bellm LA, Epstein JB, Rose-Ped A, Martin P, Fuchs HJ (2000) Patient Reports of Complications of Bone Marrow Transplantation. Support Care Cancer 8:33-9.
29. Lee L, Smith-Whitley K, Banks S, Puckrein G (2019) Reducing Health Care Disparities in Sickle Cell Disease: A Review. Public Health Rep 134:599-607.
30. Krishnamurti L, Arnold SD, Haight A, Abraham A, Guilcher GM, John T, et al.. (2022) Sickle Cell Transplantation Evaluation of Long-term and Late Effects Registry (STELLAR) to Compare Long-term Outcomes After Hematopoietic Cell Transplantation to Those in Siblings Without Sickle Cell Disease and in Nontransplanted Individuals with Sickle Cell Disease. MIR Res 2:1-11.
31. Kanter J, Falcon C (2021) Gene Therapy for Sickle Cell Disease: Where We Are Now? Emerging Therapies and Considerations for Sickle Cell Disease 174:174-8.
32. Ribeil J-A, Hacein-Bey-Abina S, Payen E, Magnani A, Semeraro M, Magrin E, et al.. (2017) Gene Therapy in a Patient with Sickle Cell Disease. N Engl J Med 376:848-55
33. Esrick EB, Lehmann LE, Biffi A, Achebe M, Brendel C, Ciuculescu M, et al.. (2021) Post-Transcriptional Genetic Silencing of BCL11A to Treat Sickle Cell Disease. N Engl J Med 384:205-15.
34. Ware RE, Aygun B (2009) Advances in the Use of Hydroxyurea. Hematology/Oncology and Stem Cell Therapy 1:62-9.
35. Singh J, Singh N, Kumar A, Kedia NB, Agarwal A (2013) Dental and Periodontal Health Status of Beta Thalassemia Major and Sickle Cell Anemic Patients: a Comparative Study. J Int Oral Health 5:53.
36. British National Formulary (2024) British Medical Association and Royal Pharmaceutical Society of Great Britain.
37. Quinn CT (2018) L-Glutamine for sickle cell anemia: more questions than answers. Blood Spotlight 132:689
38. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al.. (2018) A Phase 3 Trial of L-Glutamine in Sickle Cell Disease. N Engl J Med 379:226-35.
39. Neumayr LD, Hoppe CC (2019) Sickle Cell Disease: Current Treatment and Emerging Therapies. Am J Manag Care 25:15
40. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado J, Friedrisch J, et al.. (2017) Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med 376:429-39
41. World Health Organization (2019) Sickle Cell Disease. Available from: https://www.afro.who.int/health-topics/sickle-cell-disease.
42. Tayyaba Rehan S, Hussain HU, Malik F, Usama RM, Tahir MJ, Asghar MS (2022) Voxelotor Versus Other Therapeutic Options for Sickle Cell Disease: Are We Still Lagging Behind in Treating the Disease? Health Sci Rep 5:e713.
43. Vichinsky E, Hoppe C, Ataga K, Ware R, Nduba V, El-Beshlawy A, et al.. (2019) A Phase 3 Randomised Trial of Voxelotor in Sickle Cell Disease. N Engl J Med 381:509-19.
44. Heeney MM, Hoppe CC, Abboud MR, Inusa B, Kanter J, Ogutu B, et al.. (2016) A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events. N Engl J Med 374:625-35.
45. Adams JR, Brambilla D (2005) Discontinuing Prophylactic Transfusions Used to Prevent Stroke in Sickle Cell Disease. N Engl J Med 353:26.
46. Hoeks M, Yu G, Langemeijer S, Crouch S, De Swart L, Fenaux P, et al.. (2020) Impact of Treatment with Iron Chelation Therapy in Patients with Lower-Risk Myelodysplastic Syndromes Participating in the European MDS Registry. Haematologica 105:640-51.

47. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al.. (2008) Opioid Complications and Side Effects. Pain Physician 11:S105-20. .

48. Gonzalez-Estrada A, Radojicic C (2015) Penicillin Allergy: A Practical Guide for Clinicians. Cleveland Clin J Med 82:295-300.

49. Nurain IO, Bewaji CO, Johnson JS, Davenport RD, Zhang Y (2017) Potential of Three Ethnomedicinal Plants as Antisickling Agents. Mol Pharm 14:172-82.

50. Ouattara B, Jansen O, Angenot L, Guissou IP, Frederich M, Fondu P, Tits M (2009) Antisickling Properties of Divanilloylquinic Acids Isolated from Fagara zanthoxyloides Lam. (Rutaceae). Phytomedicine 16:125-9.

51. Wambebe C, Khamofu H, Momoh JAF, Ekpeyong M, Audu BS, Njoku OS, et al.. (2001) Double-Blind, Placebo-Controlled, Randomized Cross-Over Clinical Trial of NIPRISAN® in Patients with Sickle Cell Disorder. Phytomedicine 8:252-61.

52. Thompson WE, Eriator I (2014) Pain Control in Sickle Cell Disease Patients: Use of Complementary and Alternative Medicine. Pain Med 15:241-6.

53. Kohli M, Kohli G (2014) Understanding of Naturopathy. Int J Nurs Educ Res 2:135-9.

54. Vickers A, Zollman C (1999) ABC of Complementary Medicine. Homoeopathy. BMJ 319:1115-8.

55. Mahmood LA, Thaniel L, Martin B, Marguiles S, Reece-Stremtan S, Idiokitas R, et al.. (2021) Integrative Holistic Approaches for Children, Adolescents, and Young Adults with Sickle Cell Disease: A Single Center Experience. Complement Ther Med 60:102680.

56. Nartey EB, Spector J, Adu-Afarwuah S, Jones CL, Jackson A, Ohemeng A, et al.. (2021) Nutritional Perspectives on Sickle Cell Disease in Africa: A Systematic Review. BMC Nutr 7:1-21.

57. Khan SA, Damanhouri G, Ali A, Khan SA, Khan A, Bakillah A, et al.. (2016) Precipitating Factors and Targeted Therapies in Combating the Perils of Sickle Cell Disease: A Special Nutritional Consideration. Nutr Metab 13:1-12.

58. Matthie N, Ross D, Sinha C, Khemani K, Bakshi N, Krishnamurti L (2019) A Qualitative Study of Chronic Pain and Self-Management in Adults with Sickle Cell Disease. J Natl Med Assoc 111:158-68.

59. Katz N (2002) The Impact of Pain Management on Quality of Life. J Pain Symptom Manage 24:S38-S47.

60. Elendu C, Amaechi DC, Alakwe-Ojimba CE, Elendu TC, Elendu RC, Ayabazu CP, et al.. (2023) Understanding Sickle Cell Disease: Causes, Symptoms, and Treatment Options. Medicine (Baltimore) 102:e35237

61. Ludwig H, Strasser K (2001) Symptomatology of Anemia. Semin Oncol 28:7-14.

62. Bull BS, Hay KL (2001) Is the Packed Cell Volume (PCV) Reliable? Lab Hematol 7:191-6.

63. Emmanuelchide O, Charle O, Uchenna O (2011) Hematological Parameters in Association with Outcomes in Sickle Cell Anemia Patients. Indian J Med Sci 65:393-8.

64. Matthie N, Ross D, Sinha C, Khemani K, Bakshi N, Krishnamurti L (2019) A Qualitative Study of Chronic Pain and Self-Management in Adults with Sickle Cell Disease. J Nat Med Assoc 111:158-68.

65. Chang CY, Schiano TD (2007) Drug Hepatotoxicity. Aliment Pharmacol Ther 25:1135-51.

66. Stournaras E, Tziomalos K (2015) Herbal Medicine-Related Hepatotoxicity. World J Hepatol 7:2189.

67. Higgins JPT, Sterne JAC, Savovic J, Page MJ, Hróbjartsson A, Boutron I, et al.. (2016) A Revised Tool for Assessing Risk of Bias in Randomised Trials. Cochrane Database Syst Rev 10:29-31.

68. Akinsulie AO, Temiye EO, Akanmu AS, Lesi FEA, Whyte CO (2005) Clinical Evaluation of Extract of Cajanus cajan (Ciklavit®) in Sickle Cell Anaemia. J Trop Pediatr 51:200-5.

69. Ballas SK (2018) Sickle Cell Disease: Classification of Clinical Complications and Approaches to Preventive and Therapeutic Management. Clin Hemorheol Microcirc 68:105-28.

70. Anie KA, Steptoe A, Bevan DH (2002) Sickle Cell Disease: Pain, Coping and Quality of Life in a Study of Adults in the UK. Br J Health Psychol 7(3):331-44.

71. Dash BP, Archana Y, Satapathy N, Naik SK (2013) Search for Antisickling Agents from Plants. Pharmacognosy Rev 7:53.

72. Mishra PK, Sharma S, Jain V, Tiwari J, Mishra M, Patra PK, Khodiar PK (2018) Antisickling and Antioxidant Relevance of Twelve Ethnomedicinal Plants. Med Plants Int J Phytomedicines Relat Ind 10:226-35.

73. Azubuike CP, Uzoeto CA, Igbokwe NH, Igwilo CI (2016) In vitro Antisickling, Antimicrobial and Antioxidant Potentials of Extracts of Sorghum bicolor (L) Moench seeds and Mangifera indica (L) Anacardiaceae leaves and Their Formulations. J Sci Pract Pharm 3:135-44.

74. Iweala EEJ, Uhegbu FO, Ogu GN (2010) Preliminary In Vitro Antisickling Properties of Crude Juice Extracts of Persia Americana, Citrus sinensis, Carica papaya and Ciklavit®. J Tradit Complement Med 7(2).

75. Giannini E, Testa R, Savarino V (2005) Liver Enzyme Alteration: A Guide for Clinicians. CMAJ 172:367-79.

76. Nathan S, Tripathi P, Wu Q, Belanger FC (2009) Nicosan: Phytomedicinal Treatment for Sickle Cell Disease. ACS Symp Ser 1021:263-76.

77. Mburu C, Kareru P, Kipyegon C, Madivoli E, Maina E, Kairigo P, et al.. (2016) Phytochemical Screening of Crude Extracts of Bridelia micrantha. Eur J Med Plants 16:1-7.

78. Famojuro TI, Moody JO (2015) Survey of Medicinal Plants Used in the Management of Sickle Cell Disease by Traditional Medical Practitioners of Gbonyin Local Government Area of Ekiti State, Nigeria. Niger J Nat Prod Med 19:10.

79. Ngueyem TA, Brusotti G, Caccialanza G, Finzi PV (2009) The Genus Bridelia: A Phytochemical and Ethnopharmacological Review. J Ethnopharmacol 124:339-49.

80. Omeh YN, Ezeja MI, Onoja SO, Ukattah EC (2014) Hypolipidemic and Hematological Effects of

Hydromethanolic Extract of the Leaves of Bridelia micrantha on Alloxan-Induced Diabetic Rats. Int J Toxicol Pharmacol Res 6:102-6.

81. Omeh YN, Ezeja MI, Onoja SO, Ukattah EC (2014) Hypolipidemic and Hematological Effects of Hydromethanolic Extract of the Leaves of Bridelia micrantha on Alloxan-Induced Diabetic Rats. Int J Toxicol Pharmacol Res 6:102-6.

82. Etono CEA, Lienou LL, Dongmo FFD, Kognou ALM, Tchientcheu R, Etame RME, Ngane RAN (2023) Acute and Sub-Chronic Toxicity Evaluation of the Crude Methanolic Bark Extract of Bridelia micrantha (Hochst.) Baill. (Phyllanthaceae) and Its Fraction. J Biosci Med 11:76-89.

83. Akakpo-Akue J, Kplr KTM, Kra AKM, Konana GKNA, Koussi KAM, Ouattara SGKJ, et al.. (2023) Phytochemical Investigation and Antisickling Properties of a Poly-Herbal Formula on the HBSS Red Blood Cells. J Pharmacogn Phytochem 12:260-5.

84. Njan AA, Iwalewa EO, Akinpelu LA, Ilesanmi OR, Diniyan OM, Fatuna OA, et al.. (2015) Analgesic Effects of Harungana madagascariensis Stem Bark Extract Using Four Experimental Models of Nociception. Ife J Sci 17:627-36.

85. Shorinwa OA, Monsi B (2020) Toxicological Implications of the Fruit of Harungana madagascariensis on Wistar Rats. Clin Phytoscience 6:1-9.

86. Biapa PCN, Oben JE, Ngogang JY (2012) Acute and Subacute Toxicity of Harungana madagascariensis LAM. Afr J Pharm Sci Pharm 3

87. Fouda Y, Tom E, Atsano A, Bonahe C, Dimo T (2020) Effects of Stem Bark Aqueous Extract of Fagara tessmannii on Cardiovascular Risks in Glutamate-Induced Obesity in Rats. J Ethnopharmacol.

88. Oyelere SF, Tunwagun DA, Bamikunle MV, Ayoade TE, Adebayo TA, Oluwatola BS, Akinyemi OA (2021) Phytochemical Analysis of Ficus thonningii: A Qualitative Study. J Med Herbs Ethnomed 7:47-51.

89. Coker ME (2014) Antimicrobial and Anti-Inflammatory Activities of Extracts of Ficus Thonningii Blume (Moraceae). [Online] Available: http://80.240.30.238/handle/123456789/797

90. Ijoma I (2023) In Vitro Antioxidant Characterization of Extracts of Ficus Thonningii, Jatropha tonjorensis and Justicea Carnea: Implication on Sickle Cell. Der Pharmacia Lettre 15:1-27

91. Ahur VM, Madubunyi I, Adenkola AY, Udem SC (2012). The Effect of Ethyl Acetate Extract of Ficus thonningii (Blume) Leaves on Erythrocyte Osmotic Fragility and Haematological Parameters in Acetaminophen-Treated Rats. Comparative Clinical Pathology. 21:409-13

92. Fokunang ET, Ngo BMOA, Ambassa PA, Legrand NNB, Ngameni B, Fokunang C (2023). Preclinical In vivo Acute Toxicity Testing of Hydroethanolic Extracts of Ficus thonningii Blume (Moraceae) on Wistar Rat Models. J Complement Altern Med Res 21:18-34.

93. Dangarembizi R, Erlwanger KH, Chivandi E (2014). Effects of Ficus thonningii Extracts on the Gastrointestinal Tract and Clinical Biochemistry of Suckling Rats. Afr J Tradit Complement Altern Med 11:285-91. .

94. Ofodile LN, Kanife UC, Arojojoye BJ (2010). Antifungal Activity of a Nigerian Herbal Plant Chrysanthellum americanum. Int J Biol Sci 3:60-63.

95. Guenné S, Ouattara N, Meda NR, Kinda PT, Ouédraogo N, Ciobica A, et al.. (2019). Relevance of Chrysanthellum americanum (L.) Vatke Extracts in Rat Liver Protection. Int J Biochem Res Rev 25:1-10.

96. Niranjan A, Prakash D (2008). Chemical Constituents and Biological Activities of Turmeric (Curcuma longa L.)—A Review. J Food Sci Technol 45:109-114.

97. Mbemba TF, Mbadiko CM, Ngbolua K-t-N, Mpiana PT, Hity M, Kikakedimau RN, et al.. (2017). Phytochemical Screening and Assessment of Anti-sickling Activity of Total Methanolic Extracts of Different Organs of Curcuma longa L. (Zingiberaceae). Pharm Chem J 4:32-40.

98. Panahi Y, et al.. (2016). The Efficacy of Curcumin in the Management of Pain: A Systematic Review. J Pain Res 9:673-684.

99. Razavi BM, Rahbardar MG, Hosseinzadeh H (2021). A Review of Therapeutic Potentials of Turmeric (Curcuma longa) and Its Active Constituent, Curcumin, on Inflammatory Disorders, Pain, and Their Related Patents. Phytother Res 35:6489-6513.

100. Chin D, Huebbe P, Frank J, Rimbach G, Pallauf K (2014). Curcumin May Impair Iron Status When Fed to Mice for Six Months. Redox Biol 28:563-569.

101. Hussain MA (2014). Comparative Study on Hematological Changes in Adult and Aged Rats after Curcumin Administration. Bull Egypt Soc Physiol Sci 34:357-366.

102. Soleimani V, et al.. (2018). Turmeric and Its Major Constituent as Nontoxic and Safe Substances. Phytother Res 32:985-995.

103. Panahi Y, et al.. (2014). Safety and Efficacy of Curcumin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Med Food 17:2-10.

104. Idris S, Ndukwe G, Gimba C (2009). Preliminary Phytochemical Screening and Antimicrobial Activity of Seed Extracts of Persea americana (Avocado Pear). Bayero J Pure Appl Sci 2:173-176.

105. Lukyamuzi JE, Aweta NOJ, Nkwangu D, Domínguez MG, Betancourt VM, Rodriguez MO (2018). Antisickling Effect of Crude Flavonoids in the Methanolic Leaf Extract of Persea americana Mill. Rev Cubana Plantas Med 23:2.

106. Kristanti CD, Simanjuntak FPJ, Dewi NKPA, Tianri SV, Hendra P (2017). Anti-inflammatory and Analgesic Activities of Avocado Seed (Persea americana Mill.). J Pharm Sci Commun 14:104-111.

107. Kristanti CD, Simanjuntak FPJ, Dewi NKPA, Tianri SV, Hendra P (2017). Anti-inflammatory and Analgesic Activities of Avocado Seed (Persea americana Mill.). J Pharm Sci Commun 14:104-111.

108. Obiandu C, Owhorji BI, Okari K, Amechi CS (2022). Actions of Persea americana on Some Blood Parameters of Male Wistar Rats. Scholars Int J Anat Physiol 5:105-109.

109. Nicolella HD, Neto FR, Corrêa MB, Lopes DH, Rondon ED, Dos Santos LFR, et al.. (2017). Toxicogenetic Study

of Persea americana Fruit Pulp Oil and Its Effect on Genomic Instability. Food Chem Toxicol 101:114-120.

110. Omolara FY, Abiodun HA, Titilope MD, Ying-Jun Z, Emeka EJI (2019). Cytotoxic Effects of Compounds Isolated from Ricinodendron heudelotii. Molecules 24:145.

111. Mpiana PT, Makelele LK, Oleko RW, Bokota MT, Tshibangu DST, Ngbolua KN, et al.. (2010). Antisickling Activity of Medicinal Plants Used in the Management of Sickle Cell Disease in the Tshopo District, DR Congo. Aust J Med Herbalism 22:132-137.

112. Henneh IT, Ahlidja W, Asiamah EA, Opoku-Kwabi DO, Korsah HM, Malcom F, et al.. (2024). Antinociceptive and Anti-Ulcerogenic Effect of Hydroethanolic Stem Bark Extract of Ricinodendron heudelotii (Baill.) Pierre ex. Heckel (Euphorbiaceae): Involvement of the Opioidergic Pathway and Attenuation of Oxidative Stress. J Tradit Complement Med.

113. Médard SF, Atchadé Pascal TA, Félicienne A, Yollande A, Roxane K, Ezéchiel LJ, et al.. (2024). Impact of the Aqueous Extract of Jatropha gossypiifolia Leaves in the Treatment of Anemia Induced in Wistar Rats. Int J Pharm Sci Invent 12:11-22.

114. Yakubu OF, Adebayo AH, Adegbite OS, Ishola TA, Imonikhe LO, Adeyemi OA, et al.. (2018). Antimicrobial and Toxicological Studies of Ricinodendron heudelotii (Baill.). Asian J Pharm Clin Res 11:299-305.

115. Usunobun U, Okolie NP (2015). Phytochemical, Trace, and Mineral Composition of Vernonia amygdalina Leaves. Int J Biol Pharm Res 6:393-399.

116. Ayuba SA, Onu A (2024). Phytochemical Analysis and Antisickling Activity of Some Medicinal Plants from Sokoto, Nigeria. UMYU Scientifica 3:130-140.

117. Njan AA, Adzu B, Agaba AG, Byarugaba D, Díaz-Llera S, Bangsberg DR (2008). The Analgesic and Antiplasmodial Activities and Toxicology of Vernonia amygdalina. J Med Food 11:574-581

118. Airaodion AI, Ekenjoku JA, Ogbuagu OE, Ogbuagu U, Airaodion EO (2019). Antihaemolytic Effect of Ethanolic Extract Leaf of Vernonia amygdalina in Wistar Rats. Int J Bio Sci Bio Technol 11:173-178.

119. Zakaria Y, Azlan NZ, Fakhruddin N, Hassan N, Muhammad H (2016). Phytochemicals and Acute Oral Toxicity Studies of the Aqueous Extract of Vernonia amygdalina from State of Malaysia. J Med Plants 4:1-5.

120. Kplé TKM, Akakpo-Akue J, Golly JK, Fofie Y, Ahon MG, Kra MA, et al.. (2020). Phytochemical Characterisation of Three Plants and Their Antisickling Activity in the Management of Sickle Cell Disease. J Biosci Med 8:100.

121. Semado FM, Tchogou AP, Agbogba F, Abissi Y, Kassa R, Lokonon J, et al.. (2023). Impact of the Aqueous Extract of Jatropha Gossypiifolia Leaves in the Treatment of Anemia Induced in Wistar Rats. Int J Pharm Sci Invent 12:11-22.

122. Amponsah IK, Opoku-Kwabi D, Armah FA, Addotey JN, Turkson BK, Kontoh EQ (2024). A Systematic Review of Medicinal Plants and Their Compounds Validated as Agents for the Management of Sickle Cell Disease. Nat Prod Commun 19.

123. Ahmed AS, Chopde CT, Kashmiri ZN (2015). Assessment Of Anti-Inflammatory and Anti-Arthritis Activity of Jatropha Gossypifolia In Rats. Int J Pharm Sci 7:258-60.

124. Magili S, Bwatanglang I (2018). Toxicity Study of Aqueous Leaves Extract of Jatropha gossypiifolia from Nigeria in Albino Rats: Serum Biochemistry and Histopathological Evaluation. Int J Biochem Res Rev 21:1-12.

125. Njinga NS, Sule MI, Pateh UU, Hassan HS, Ahmad MM, Abdullahi ST, et al.. (2014). Phytochemical and Antimicrobial Activity of the Leaves of Lannea kerstingii Engl & K. Krause (Anacadiaceae). J Health Allied Sci NU 4:4-9.

126. Magnang H, Mawussi K, Layibo Y, Vovor A, Agbonon A (2021). Knowledge and Therapeutic Use of Lannea Kerstingii and Pavetta corymbosa by Sickle Cell Patients and Pregnant Women in Lomé (Togo). RAMReS Rev Pharm Series Afr TradMed 20:18-23.

127. Magnang H, Kueviakoé MDI, Togbenou K, Agbonon A (2023). Effect of Hydromethanolic Extract of Stem Bark of Lannea kerstingii on Anemia and Hepcidin Production. J Drug Deliv Ther 13:70-4.

128. Diallo A, Eklu-Gadegbeku K AA, Aklikokou K, Napo-Koura G, Creppy E, Gbeassor M (2015). Repeated-Dose Toxicological Studies of Hydroalcoholic Extract of Lannea kerstingii Engl and K. Krause (Anacardiaceae) and Identification of Toxicity Mechanisms. Int J Pharm Sci Res 6:604-611

129. Diallo A, Darre P, Metowogo K, Lawson-evi P, Selva D, Potchoo Y, et al.. (2016). Fetal Toxicity and Cytotoxicity of Lannea kerstingii Engl and Krause Stem Bark (Anacardiaceae). Trop J Pharm Res 15:253-8.

130. Oukparigha FO, Nyananyo BL, Oyedeji AA (2019). Evaluation of the Bioactive Compounds in Leaves and Stem-Bark of Piptadeniastrum Africanum (Hook. F.) Brenan (Family Fabaceae). Int J Med Plants Nat Prod 5:1-7.

131. Chisom UV, Oluwasey OE (2022). Investigating the Analgesic Property of Piptadeniastrum africanum (Mimosaceae) Using Formalin-Induced Pain Model. Int J Acad Res 8:81-93.

132. Dlamini LM, Tata CM, Djuidje MCF, Ikhile MI, Nikolova GD, Karamalakova YD, et al.. (2019). Antioxidant and Prooxidant Effects of Piptadeniastrum africanum as the Possible Rationale Behind its Broad Scale Application in African Ethnomedicine. J Ethnopharmacol 231:429-37.

133. Olojo FO (2023). Isolation of Stigmasterol from Piptadeniastrum africanum (Hook. F.) and Its Modulatory Effect On Mitochondrial-Mediated Cell Death In Liver and Colonic Toxicity in Mice. UI Postgraduate College, 2023.

134. Ojogu NA, Annune PA, Okayi GR (2017). Toxicological Effects of Aqueous Extract of Piptadeniastrium africanum Bark on Clarias gariepinus Juveniles. Banat J Biotechnol 8:123.

135. Adeniyi O, Baptista R, Bhowmick S, Cookson A, Nash RJ, Winters A, et al.. (2022). Isolation and Characterisation of Quercitrin as a Potent Anti-Sickle Cell Anaemia Agent from Alchornea cordifolia. J Clin Med 11:2177.

136. Pone Kamdem Boniface, Sabrina Baptista Ferreira, Carlos Roland Kaiser. (2016). Recent Trends in Phytochemistry,

Ethnobotany, and Pharmacological Significance of Alchornea cordifolia (Schumach. & Thonn.) Muell. Arg. J Ethnopharmacol 191:216-244.

137. Ishola IO, Ashorobi RB, Adeoluwa O (2012). Evaluation of the Antinociceptive Activities of the Aqueous Root Extract of Alchornea cordifolia (Schumach and Thonn) Müll. Arg. (Euphorbiaceae). 5:37-42.

138. Ezugwu HC, Jankada PA, Ipav SS, Dasofunjo K (2022). Anti-Anaemic and Hepato-Renal Activities of Ethanol Extract of Alchornea cordifolia in Phenyl Hydrazine Induced-Anaemic Wistar Rats. Glob J Pure Appl Sci 28:2.

139. Ansah C, Oppong E, Woode E, Duwiejua M (2009). Toxicity Studies on Alchornea cordifolia Leaf Extract in Mice. J Sci Technol Ghana 29:8-16.

140. Akhtar MF, Sharif A, Saleem M, Saleem A, Akhtar B, Raza M, et al.. (2017). Genotoxic and Cytotoxic Potential of Alternanthera Bettzickiana, an Important Ethno-Medicinal Plant. Cell Mol Biol 63:109-14.

141. Kitadi JM, Inkoto CL, Lengbiye EM, Tshibangu DST, Tshilanda DD, Ngbolua KN, et al.. (2019). Antisickling Activity and Mineral Content of Hura crepitans L., Alternanthera bettzickiana (Regle) G. Nicholson, and Dissotis brazzae Cogn, Plants Used in the Management of Sickle Cell Disease. Eur J Pharm Med Res 6:79-83.

142. Manan M, Saleem U, Akash MSHA, Qasim M, Hayat M, Raza Z, Ahmad B (2020). Anti-Arthritic Potential of Comprehensively Standardised Extract of Alternanthera bettzickiana: In Vitro and In Vivo Studies. ACS Omega 5:19478-96.

143. Kasthuri OR, Ramesh B (2018). Toxicity studies on leaf extracts of Alternanthera brasiliana (L.) Kuntze and Alternanthera bettzickiana (Regel) Voss. Journal of Applied Pharmaceutical Science. 8:082-9.

144. Diallo D, Dramé A, Niang L, Badock EA, Diallo I, Sow S, Ayessou NC (2024). Phytochemical Screening and Antioxidant Activity of Annona Senegalensis Extracts (Leaves and Stem Bark) Collected from Three Regions of Senegal. Advances in Biochemistry. 12:105-11.

145. Bongo G, Inkoto C, Masengo C, Tshiama C, Lengbiye E, Djolu R, et al.. (2017). Antisickling, Antioxidant and Antibacterial Activities of Afromomum alboviolaceum (Ridley) K. Schum, Annona senegalensis Pers. and Mondia whitei (Hook. f.) Skeels. American Journal of Laboratory Medicine. 2:52-9

146. Mpiana PT, Dianzenza EN, Ngbolua KN, Tshibangu DST, Mbala BM, Mhigo SO, et al.. (2012). Antisickling Properties, Thermal and Photochemical Degradations of Anthocyanin Extracts from Annona senegalensis (Annonaceae). International Journal of Biological and Chemical Sciences. 6:2241-51.

147. Adzu B, Amos S, Adamu M, Gamaniel KS (2003). Anti-nociceptive and Anti-Inflammatory Effects of the Methanol Extract of Annona senegalensis Root Bark. Journal of Natural Remedies. 3:63.

148. Mbaya YP, Bobbo AG, Barkindo AA, Hayatu AI (2023). Toxicity and the Effects of Ethanolic Leaf Extract of Annona senegalensis on Haematological Parameters in Albino Rats. British Journal of Multidisciplinary and Advanced Studies. 4:81-100.

149. Okoye TC, Akah PA, Ezike AC, Okoye MO, Onyeto CA, Ndukwu F, et al.. (2012). Evaluation of the Acute and Sub-Acute Toxicity of Annona senegalensis Root Bark Extracts. Asian Pacific Journal of Tropical Medicine. 5:277-82.

150. Sudipta KM, Lokesh P, Rashmi W, Vijay R, Kashyap Ssn (2012). Phytochemical Screening and in vitro Antimicrobial Activity of Bougainvillea spectabilis flower extracts. International Journal of Phytomedicine. 4:375.

151. Mpiana PT, Mudogo V, Tshibangu D, Kitwa EK, Kanagila AB, Lumbu JBS, et al.. (2008). Antisickling Activities of Anthrocyanins from Bombax pentadrum, Ficus capensis and Ziziphus mucronata: Photodegradation Effect. Journal of Ethnopharmacology. 120:413-8.

152. Castañeda-Corral G, Cedillo-Cortezano M, Aviles-Flores M, López-Castillo M, Acevedo-Fernández JJ, Petricevich VL (2024). Antinociceptive and Anti-Inflammatory Activities of Acetonic Extract from Bougainvillea x buttiana (var. Rose). Pharmaceuticals. 17:1037.

153. Adebayo JO, Adesokan AA, Olatunji LA, Buoro DO, Soladoye AO (2005). Effects of Ethanolic extract of Bougainvillea spectabilis leaves on Haematological and Serum Lipid Variables in Rats. Biokemistri. 17:45-50.

154. Teh LE, Kue CS, Ng CH, Lau BF (2019). Toxicity Effect of Bougainvillea glabra (Paper Flower) Water Extracts on Zebrafish Embryo. INNOSC Theranostics and Pharmacological Sciences. 2:25-8.

155. Yeboah GN, Owusu FWA, Archer M-A, Kyene MO, Kumadoh D, Ayertey F, et al.. (2022). Bridelia ferruginea Benth.; An Ethnomedicinal, Phytochemical, Pharmacological and Toxicological Review. Heliyon. 8.

156. Jain S, Vaidya A, Shah K, Chauhan DN, Chauhan NS (2019). Anti-sickling Herbs. Plant and Human Health. 3:255-83.

157. Akuodor GC, Mbah CC, Anyalewechi NA, Idris-Usman M, Iwuanyanwu TC, Osunkwo UA (2011). Pharmacological Profile of Aqueous extract of Bridelia ferruginea Stem Bark in the Relief of Pain and Fever. Journal of Medicinal Plants Research. 5:5366-9.

158. Oladejo AA, Osukoya O (2021). Hematological profiles of naturally infected pigs treated with Bridelia ferruginea leaf extracts. Asian Hematology Research Journal. 4:1-10.

159. Bakoma B, Berké B, Eklu-Gadegbeku K AA, Aklikokou K, Gbeassor M, Creppy EE, Moore N (2013). Acute and Sub-Chronic (28 days) Oral Toxicity Evaluation of Hydroethanolic Extract of Bridelia ferruginea Benth Root Bark in Male Rodent Animals. Food and Chemical Toxicology. 52:176-9.

160. Wahua C, Okoli BE, Sam SM (2013). Comparative Morphological, Anatomical, Cytological and Phytochemical Studies on Capsicum frutescens Linn. and Capsicum annuum Linn. (Solanaceae). International Journal of Scientific & Engineering Research. 4:1-11.

161. Jolayemi AT, Ojewole JAO (2013). Comparative anti-inflammatory properties of Capsaicin and ethylacetate extract of Capsicum frutescens linn [Solanaceae] in rats. African Health Science. 13:357-61.

162. AL-Qarawi AA, Adam SEI (2003). Effect of Combination of Capsicum frutescens and Citrullus colocynthis on growth, haematological and pathophysiological parameters of rats. Phytotherapy Research. 17:92-5

share
Send us an email: hsijournal@ug.edu.gh
Visit us: https://www.hsijournal.ug.edu.gh

163. AL-Qarawi AA, Adam SEI (2003). Effect of combination of Capsicum frutescens and Citrullus colocynthis on growth, haematological and pathophysiological parameters of rats. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 17:92-95.

164. Wadekar A, Nimbalwar MG, Panchale WA, Gudalwar BR, Manwar JV, Bakal RL (2021). Morphology, Phytochemistry and Pharmacological Aspects of Carica papaya, a Review. GSC Biological and Pharmaceutical Sciences. 14:234-48.

165. Imaga NA, Gbenle GO, Okochi VI, Adenekan S, Duro-Emmanuel T, Oyeniyi B, et al.. (2010). Phytochemical and Antioxidant Nutrient Constituents of Carica papaya and Parquetina nigrescens Extracts. Academic Journals.

166. Mojisola OC, Adebolu EA, Alani DM (2008). Antisickling properties of Carica papaya Linn. Journal of Natural Products. 1:56-8.

167. Hasimun P, SUwendar, Ernasari GI (2014). Analgetic activity of Papaya (Carica papaya L.) Leaves Extract. Procedia Chemistry. 13:147-9.

168. Adewuyi HA, Kabiru AY, Muhammad HL, Lukman HY, Owolabi MS, Jonathan I, Lawal B (2024). Pre-Clinical Protective Potentials of Carica papaya Constituents in Experimentally Induced Anemia. American Journal of Translational Research. 16:3259.

169. Eliagita C, Kuntjoro T, Sumarni S, Suwondo A, Hadisaputro S, Eliagita C, Mulyantoro DK (2017). Effect of Consuming Papaya (Carica papaya Linn.) on the Level of Hemoglobin and Hematocrit in Pregnant Women with Anemia. Belitung Nursing Journal. 3:120-5.

170. Halim SZ, Abdullah NR, Afzan A, Abdul Rashid B, Jantan I, Ismail Z (2011). Acute Toxicity Study of Carica papaya Leaf Extract in Sprague Dawley Rats. Journal of Medicinal Plants Research. 5:1867-72.

171. Nondo RSO, Moshi MJ, Erasto P, Masimba PJ, Machumi F, Kidukuli AW, et al.. (2017) Anti-Plasmodial Activity of Norcaesalpin D and Extracts of Four Medicinal Plants Used Traditionally for Treatment of Malaria. BMC Complementary and Alternative Medicine 17:1-8.

172. Kitadi JM, Mazasa PP, Tshibangu DST, Memvanga PB, Ngbolua KN, Taba NK, et al.. (2015) Anti-sickling and Antioxidant Activities of Anthocyanins Extracts from Dissotis brazzae Cogn. (Melastomataceae). Journal of Advancement in Medical and Life Sciences 3:1-6.

173. Moshi MJ, Innocent E, Masimba PJ, Otieno DF, Weisheit A, Mbabazi P, et al.. (2009) Antimicrobial and brine shrimp toxicity of some plants used in traditional medicine in Bukoba District, north-western Tanzania. Tanzania Journal of Health Research 11:1.

174. Onwuka OM, Nwaka AC, Ezeanyanwu VC (2024) Comparative Study on the Effects of Consumption of Garcinia kola and Cola acuminata on Some Biochemical Parameters of Wistar Albino Rats. IPS Journal of Nutrition and Food Science 3:178-91.

175. Adejumo OE, Ayoola MD, Kolapo AL, Orimoyegun VO, Olatunji PO (2011) Antisickling Activities of Extracts of Leaf, Seed and Seed Pod of Garcinia kola Heckel. African Journal of Pharmacy and Pharmacology 5:48-52.

176. Olayinka OA, Adesanya SA, Idowu TO, Okimi OC, Oyelami OA, Iwalewa EO (2008) Clinical effects of Garcinia kola in knee osteoarthritis. Journal of Orthopaedic Surgery and Research 3:1-10.

177. Omoirri MA, Chukwuemeka CO, Uyovwiesevwa AJ, Maduka KI, Orji UH (2022) Hematological Changes in Administration of Garcinia Kola Seed Extract to Wistar Rats. Clinical Research Notes 3:2.

178. Ibrahim H, Sani FS (2006) Phytochemical and Antisickling Studies of Hymenocardia acida Tul (Euphorbiaceae). East and Central African Journal of Pharmaceutical Sciences 9:58-59.

179. Olotu PN, Olotu IA, Kambasha MB, Ahmed A, Ajima U, Ohemu TL, Okwori VA, Dafam DG, Agwom FM, David J, Onche EU (2017) Nutritional effects, toxicity and haematology studies of the ethanolic root bark extract of Hymenocardia acida, Tul (Euphorbiaceae). Journal of Applied Pharmaceutical Science 7:111-114.

180. Olotu PN, Olotu IA, Kambasha MB, Ahmed A, Ajima U, Ohemu TL, et al.. (2017) Nutritional Effects, Toxicity and Haematology Studies of the Ethanolic Root Bark Extract of Hymenocardia acida, Tul (Euphorbiaceae). Journal of Applied Pharmaceutical Science 7:111-114.

181. Sofidiya MO, Adedapo AA, Jimoh FO, Masika PJ, Afolayan AJ, Odukoya OA, Familoni OB (2010) Safety Evaluation of Hymenocardia Acida Leaf Extracts in Rats and Mice. 3:90-95.

182. Sofidiya MO, Odukoya OA, Adedapo AA, Mbagwu HOC, Afolayan AJ, Familoni OB (2010) Investigation of the anti-inflammatory and antinociceptive activities of Hymenocardia acida Tul. (Hymenocardiaceae). African Journal of Biotechnology 9:8454-8459.

183. Nsibande BE, Gustavsson K-E, Li-Hua Zhu L-H (2018) Analysis of Health-Associated Phytochemical Compounds in Seven Hypoxis Species. American Journal of Plant Sciences 9:571-583.

184. Kitadi JM, Inkoto CL, Tshibangu S-T, Tshilanda DD, Taba Kalulu, Kawata P, et al.. (2022) Mineral Element Contents and Antisickling Activity of Cyttaranthus congolensis and Hypoxis angustifolia Traditionally Used to Treat Sickle Cell Disease in Kwilu Province. International Journal of Biochemistry Research & Review 31:81-90.

185. Mpiana PT, Misakabu FM, Kitadi JM, Ngbolua KN, Tshibangu DST, Lombe BK, et al.. (2014) Antisickling activity and physico-chemical stability of anthocyanin extracts from Hypoxis angustifolia Lam. (Hypoxidaceae) bulbs. In: Noboru M, Ed., Anthocyanins: Occurrence, Structure, Biosynthesis and Health benefits Based on their Evidences of Phytochemicals in Vegetables and Fruits, Vol. 2, NOVA Science Publishers, Inc.

186. Usman H, Osuji JC (2007) Phytochemical and in vitro antimicrobial assay of the leaf extract of Newbouldia laevis. African Journal of Traditional, Complementary and Alternative Medicines 4:476-480.

187. Dermane A, Kpegba K, Metowogo K, Joppa MK, AK A (2019) Antisickling activity evaluation of fractions obtained from whole extracts of Newbouldia Laevis P. BEAUV (Bignoniaceae). International Journal of Pharmaceutical Sciences 11:42-46.

188. Dermane A, Kpegba K, Metowogo K, Joppa MK, Eklu-Gadegbeku K, Aklikokou AK, Gbeassor M (2018) Evaluation of the Anti-Sickling Activity of Newbouldia laevis P. Beauv extracts. International Journal of Biological and Chemical Sciences 12:2808-2817.

189. Ukwubile CA, Ikpefan EO, Dibal MY, Umeano VA, Menkiti DN, Kaosi CC, et al.. (2023) Pharmacognostic Profiles, Evaluation of Analgesic, Anti-Inflammatory and Anticonvulsant Activities of Newbouldia laevis (P. Beauv.) Seem. ex Bureau Leaf and Root Extracts in Rats. Journal of Ethnopharmacology 314:116632.

190. Ainooson GK, Woode E, Obiri DD, Koffour GA (2009) Antinociceptive Effects of Newbouldia laevis (P. Beauv.) Stem Bark Extract in a Rat Model. Pharmacognosy Magazine 5:17.

191. Eluu SC, Oko AO, Eluu K, Okoye CS, Onyekwere UU, Omoniyi OA (2023) Impact of Newbouldia laevis Root Extract on Hematological Parameters in Rats: A Comprehensive Study on Dosage-Dependent Effects and Long-Term Dynamics. Nigeria Agricultural Journal 54:324-329.

192. Murtala AA, Akindele AJ, IA O (2024) Ninety-Day Toxicological Assessment of Preparation of the Medicinal Plant Newbouldia laevis (P. Beauv.) Seem. (Bignoniaceae) in Rats. Natural Product Communications 19:5.

193. Mgbemene CN, Ohiri FC (1999) Anti-sickling potential of Terminalia catappa Leaf Extract. Pharmaceutical Biology 37:152-154.

194. Ujong UP, Kayode D, Saturday U, Ukorebi A, Ikenna NV (2023) Hematopoietic Effect of Aqueous Extract of Terminalia catappa Leaf in Phenyl Hydrazine Induced Hemolytic Anemia in Wistar Rats. International Journal of Biochemistry Research & Review 32:23-32.

195. Aimola I, Inuwa HM, Nok AJ, Mamman AI, Habila N, Muhammad A, et al.. (2012) Erythropoietic and Bone Marrow Stimulating Activity of Terminalia catappa extract: Possible Role of Nitric Oxide Signaling. International Blood Research & Reviews 1:1-13.

196. Arjariya S, Nema N, Tiwari S (2013) Investigate the toxicological effect on aqueous extract of Terminalia catappa linn. in rat. International Journal of Research and Development in Pharmacy and Life Sciences 2:596-601.

197. Osabor VN, Ogar DA, Okafor PC, Egbung GE (2009) Profile of the African breadfruit (Treculia africana). Pakistan Journal of Nutrition 8:1005-1008.

198. Asuelimen OS, Ogunma B, Benjamin G (2020) Proximate Composition, Preliminary Qualitative and Quantitative Phytochemical Screenings of Treculia Africana. African Journal of Biology and Medical Research 3:33-43.

199. Mpiana PT, Ngbolua KN, Mudogo V, Tshibangu DST, Atibu EK, Mbala BM, et al.. (2012) The Potential Effectiveness of Medicinal Plants used for the Treatment of Sickle Cell Disease in the Democratic Republic of Congo Folk Medicine: A Review. Progress in Traditional and Folk Herbal Medicine 1:1-12.

200. Awe JO, Osukoya OA, Adewale OB, Obafemi TO, Afolabi OB, A. K (2022) Antinociceptive effects of Treculia africana decne (African breadfruit) seed lectin in Wistar rats. ScienceRise Pharmaceutical Science 40:43-50.

201. Nwankpa P, Chukwuemeka OG, Ekweogu CN (2017) Investigation of Ethanol Stem Bark Extract of Treculia africana on the Haematological Parameters of Albino Wistar Rats. Biochemistry Analytical Biochemistry 6:2161-1009.

202. Ajayi IA, Olaifa FE, DA. R (2013) Evaluation of Nutritional and Toxicological Effects of Treculia africana (Decne.) seed Flour-Supplemented Diets on Clarias gariepinus (African catfish) fingerlings. Food Science and Quality Management 17:62-70.

203. Adeniran OA, Kuku A, Obuotor ME, Agboola FK, Famurewa AJ, Osasan S (2009) Purification, Characterisation and Toxicity of a Mannose-Binding Lectin from the Seeds of Treculia africana plant. Toxicological & Environmental Chemistry 91:1361-74.

204. Ahmed M, Hassan MM (2020) Vigna unguiculata (L.) Walp. (Papilionaceae): A review of medicinal uses, Phytochemistry and pharmacology. Journal of Pharmacognosy and Phytochemistry 9:1149-52.

205. Simeone EI, Tufon EN, Victor ON, Noel NN (2012) Antisickling potential of the ethanol seed extracts of Vigna unguiculata and Vigna subterranea. International Journal of Biochemistry and Biotechnology 1:226-29.

206. Kitadi JM, Inkoto CL, Lengbiye EM, Tshibangu DST, Tshilanda DD, Ngbolua K-T-N, et al.. (2020) Mineral Content and Antisickling Activity of Annona senegalensis, Alchornea cordifolia and Vigna unguiculata Used in the Management of Sickle Cell Disease in the Kwilu Province. International Blood Research & Reviews 11:18-27.

207. Mpiana PT, Mudogo V, Ngbolua KN, Tshibangu DST, Atibu EK, Kitwa EK, Kanangila AB (2009) In vitro antisickling activity of anthocyanins extracts of Vigna unguiculata (L.) Walp. Chemistry and medicinal value. Houston: Studium Press LLC. 75-82.

208. Adegbuyi AT, Akanmu MA, Olayiwola G, Sijuade AO (2020) Analgesic Effects of Vigna unguiculata subsepecies dekindtiana in Mice. Journal of Advances in Medical and Pharmaceutical Sciences 22:10-22.

209. Pereira EJ, Carvalho LMJ, Dellamora-Ortiz GM, Cardoso FNS, Carvalho JLV, Viana DS, Freitas SC, Rocha MM (2014) Effects of cooking methods on the iron and zinc contents in cowpea (Vigna unguiculata) to combat nutritional deficiencies in Brazil. Food & Nutrition Research 58:20694.

210. Okwunakwe F, Saidu Y, Achor M, Isa SA, Abbas AY, Bilbis LS (2020) Toxicity Studies on Aqueous-Methanol Pod Extract of Vigna unguiculata (Cowpea) in Wistar Strain Albino Rats. Nigerian Journal of Basic and Applied Sciences 28:1-9.