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Oniyangi O, Cohall DH.
Phytomedicines (medicines derived from plants) for sickle cell disease.
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD004448.
DOI: [10.1002/14651858.CD004448.pub6](https://doi.org/10.1002/14651858.CD004448.pub6).

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[Intervention Review]

Phytomedicines (medicines derived from plants) for sickle cell disease

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ABSTRACT

Background

Sickle cell disease, a common recessively inherited haemoglobin disorder, affects people from sub-Saharan Africa, the Middle East, Mediterranean basin, Indian subcontinent, Caribbean and South America. It is associated with complications and a reduced life expectancy. Phytomedicines (medicine derived from plants in their original state) encompass many of the plant remedies from traditional healers which the populations most affected would encounter. Laboratory research and limited clinical trials have suggested positive effects of phytomedicines both in vivo and in vitro. However, there has been little systematic appraisal of their benefits. This is an update of a Cochrane Review first published in 2004, and updated in 2010, 2013, and 2015.

Objectives

To assess the benefits and risks of phytomedicines in people with sickle cell disease of all types, of any age, in any setting.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register, the International Standard Randomised Controlled Trial Number Register (ISRCTN), the Allied and Complimentary Medicine Database (AMED), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

Dates of most recent searches: Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register: 10 April 2017; ISRCTN: 26 July 2017; AMED: 24 August 2017; ClinicalTrials.gov: 02 August 2017; and the WHO ICTRP: 27 July 2017.

Selection criteria

Randomised or quasi-randomised trials with participants of all ages with sickle cell disease, in all settings, comparing the administration of phytomedicines, by any mode to placebo or conventional treatment, including blood transfusion and hydroxyurea.

Data collection and analysis

Both authors independently assessed trial quality and extracted data.

Main results

Two trials (182 participants) and two phytomedicines Niprisan[®] (also known as Nicosan[®]) and Ciklavit[®] were included. The Phase IIB (pivotal) trial suggests that Niprisan[®] was effective in reducing episodes of severe painful sickle cell disease crisis over a six-month period (low-quality evidence). It did not affect the risk of severe complications or the level of anaemia (low-quality evidence). No serious adverse effects were reported. The single trial of *Cajanus cajan* (Ciklavit[®]) reported a possible benefit to individuals with painful crises (low-quality evidence), and a possible adverse effect (non-significant) on the level of anaemia (low-quality evidence).

Authors' conclusions

While Niprisan[®] appeared to be safe and effective in reducing severe painful crises over a six-month follow-up period, further trials are required to assess its role in the management of people with sickle cell disease and the results of its multicentre trials are awaited. Currently no conclusions can be made regarding the efficacy of Ciklavit[®]. Based on the published results for Niprisan[®] and in view of the limitations in data collection and analysis of both trials, phytomedicines may have a potential beneficial effect in reducing painful crises in sickle cell disease. This needs to be further validated in future trials. More trials are required on the safety and efficacy of phytomedicines used in managing sickle cell disease.

PLAIN LANGUAGE SUMMARY

Phytomedicines (medicines derived from plants) for sickle cell disease

Review question

We reviewed the evidence about the effect and safety of phytomedicines in people with sickle cell disease of all types, of any age, in any setting.

Background

Sickle cell disease is an inherited blood condition caused by defects in the production of haemoglobin. Haemoglobin is the part of the red blood cell that carries oxygen across the body. Sickle cell disease occurs when people inherit faulty genes responsible for producing haemoglobin from both parents. A variety of complications and a reduced life expectancy are linked with sickle cell disease. Phytomedicines are medicines derived from plants in their original state. People with sickle cell disease may come across them in terms of plant-remedies from traditional healers. Their benefits have not been evaluated systematically. Laboratory work has long suggested that these medicines may help to ease the symptoms of sickle cell disease.

Search date

The evidence is current to: 24 August 2017.

Study characteristics

Two trials (182 participants) and two phytomedicines Niprisan[®] (also known as Nicosan[®]) and Ciklavit[®] were included.

Key results

This review found that Niprisan[®] may help to reduce episodes of sickle cell disease crises associated with severe pain. Ciklavit[®], which has been reported to reduce painful crises in people with sickle cell disease, deserves further study before recommendations can be made regarding its use. The trial of Ciklavit[®] also reported a possible adverse effect on the level of anaemia. Both formulations reported no serious adverse symptoms or derangement of liver or kidney function in the participants. More detailed and larger trials of these medicines will need to be carried out before we can make any recommendations about their use. Further research should also assess long-term outcome measures.

Quality of the evidence

We judged the quality of the evidence from this review to be of low to very low quality, depending on the outcome measured.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings - Niprisan® versus placebo for sickle cell disease

Niprisan® compared with placebo for sickle cell disease

Patient or population: adults and children with sickle cell disease

Settings: outpatients

Intervention: Niprisan®

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Niprisan®				
Frequency, severity or duration of painful crises: frequency of mild, moderate and severe pain episodes Follow-up: 6 months	There were significantly fewer severe pain episodes in the Niprisan® group (n = 34, mean (SD): 7.9 (8.4)) compared to the placebo group (n = 36, mean (SD): 21.1 (32.9)). No statistically significant difference was noted between groups as regards mild or moderate pain in the first six-month period.		NA	70 (1 cross-over study) ¹	⊕⊕⊕⊖ low ^{2,3}	Data were skewed so not entered into analysis for this review.
Frequency of severe complications of SCD Follow-up: 6 months	No statistically significant difference in frequency of severe complications by treatment group		NA	70 (1 cross-over study) ¹	⊕⊕⊕⊖ low ^{2,3}	No separate information is provided on sequestration crises, sickle chest or leg ulcer.
Frequency of hospital admissions from severe complications of SCD Follow-up: 6 months	No statistically significant difference in frequency of hospital admissions due to severe complications (per month) by treatment group		NA	70 (1 cross-over study) ¹	⊕⊕⊕⊖ low ^{2,3}	No separate information is provided on sequestration crises, sickle chest or leg ulcer.
Any adverse events including hepatic and renal toxicity	There were no significant differences between treatment groups in adverse events reported, in terms of		NA	up to 80 (1 cross-over study) ¹	⊕⊕⊕⊖ low ^{2,3}	Specific adverse events were not reported by treatment period so are

Follow-up: 6 months	liver and renal function or in terms of serum creatinine levels.				not entered into analysis in this review.
Frequency of blood transfusion	Outcome not reported		NA	NA	
Follow-up: NA					
Level of anaemia: change in level of haemoglobin (g/dL)	The mean haemoglobin level was 8.6 g/dL in the placebo group.	The mean haemoglobin level was 0.3 g/dL higher (1.83 g/dL lower to 2.43 g/dL higher) in the Niprisan® group compared to the placebo group.	NA	52 (1 cross-over study) ¹	⊕⊕⊕⊖ low ^{2,3}
Follow-up: 6 months					
Quality of life measures: self reported health, absence from work or school	Participants in the Niprisan® group reported health being below average a mean (SD) of 12.2 (11.6) times (n = 34) compared to a mean (SD) of 31.3 (31.4) times in the placebo group (n = 36). This difference was not statistically significant.		NA	70 (1 cross-over study) ¹	⊕⊕⊕⊖ very low ^{2,3,4}
Follow-up: 6 months	There was no significant difference between treatment groups as regards absenteeism from work or school.				Data after the first cross-over period considered and no significant differences observed between groups.

*The basis for the **assumed risk** is the event rate in the control groups. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not applicable; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. One cross-over study included with 82 people randomised and followed up for one year, first period data only (up to 6 months) entered.
2. Downgraded once due to risk of bias: unclear details regarding whether an intention to treat analysis was used, randomisation methods (generation of allocation sequence).
3. Downgraded once due to applicability: study includes only individuals with HbSS genotype, not applicable to individuals with other genotypes.

4. Downgraded once due to applicability: quality of life was measured as self reported health diaries, rather than via validated questionnaires.

Summary of findings 2. Summary of findings - Ciklavit® versus placebo for sickle cell disease

Ciklavit® compared with placebo for sickle cell disease

Patient or population: adults and children with sickle cell disease

Settings: outpatients

Intervention: Ciklavit®

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ciklavit®				
Frequency, severity or duration of painful crises Follow-up: 6 months	They reported there were 207 episodes of painful crises (mean 4.4, SD 10.3) before the study, and there were 191 episodes of painful crises (mean 4.2, SD 4.2) in the Ciklavit® group and 164 episodes (mean 3.9, SD 4.3) in the placebo group.		NA	87 (1 study)	⊕⊕⊕⊕ low ^{1,2}	Data were skewed so not entered in- to 'Data and analyses' section for this review.
Frequency of severe complications of SCD Follow-up: NA	Outcome not reported			NA	NA	
Frequency of hospital admissions from severe complications of SCD Follow-up: NA	Outcome not reported			NA	NA	
Any adverse events including hepatic and renal toxicity Follow-up: 6 months	There were no significant differences between the groups regarding the following transient adverse events; vomiting, tiredness, abdominal distention, peri-orbital swelling, diarrhoea and itching of the eyes. There were also no significant differences between groups in terms of bilirubin, urea or creatinine during the study.		NA	87 (1 study)	⊕⊕⊕⊕ low ^{1,2}	

Frequency of blood transfusion	Outcome not reported			NA	NA	
Follow-up: NA						
Level of anaemia: packed cell volume	The mean packed cell volume was 22.78% in the placebo group.	The mean packed cell volume was 1.54% lower (3.16 lower to 0.08 higher) in the Ciklavit® group compared to the placebo group. This difference was not statistically significant.	NA	87 (1 study)	⊕⊕⊕⊕ low ^{1,2}	There was also no significant difference between treatment groups at 3 months, MD -1.52% (95% CI -3.49 to 0.45).
Follow-up: 6 months						
Quality of life measures	Outcome not reported			NA	NA	
Follow-up: NA						

*The basis for the **assumed risk** is the event rate in the control groups. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **NA:** not applicable; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to risk of bias: concerns regarding lack of blinding of clinicians and unclear details regarding whether an intention to treat analysis was used and if outcome measures were validated.
2. Downgraded once due to applicability: study includes only children with HbSS genotype, not applicable to adults or individuals with other genotypes.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a common recessively inherited disorder of haemoglobin affecting peoples originating from sub-Saharan Africa, the Middle East and Mediterranean basin, the Indian subcontinent, the Caribbean and South America. Descendants of immigrants from the above geographical areas, living in other parts of the world may also inherit the gene and be affected. It is estimated that 1 in 50 people in sub-Saharan Africa suffers from SCD (Davies 1997; Hickman 1999). Due to migration, persons affected with SCD are now found globally. A recent study estimates that 312,302 babies were delivered with SCD in 2010 (Piel 2013), the greatest burden of disease globally was found in three countries: Nigeria; Democratic Republic of Congo (DRC); and India. Furthermore, 75.5%, 16.9% and 4.6% of babies affected by SCD are born in sub-Saharan Africa, Arab-India, and the Americas respectively (Piel 2013).

The homozygous state - sickle cell anaemia (SS) which occurs when a person has inherited two abnormal sickle genes (one from each parent) is a more severe form of the disease. Sickle cell disease has varying clinical manifestations and is associated with complications and a reduced life expectancy (Platt 1994). Clinically significant disease also occurs in individuals who inherit the sickle gene from one parent and another variant haemoglobin gene from the second parent such as haemoglobin C (SC) or a β -thalassaemia gene (S β + or S β O) (Platt 1994; Serjeant 2001).

In SCD, haemoglobin (the part of the red blood cell that carries oxygen around the body) is abnormal. The red blood cell polymerizes (distort or change shape and become rigid) when giving up oxygen and this can lead to the blockage of small blood vessels, which in turn can stop oxygen delivery to the tissues, causing pain or organ damage (which includes the liver, lungs and kidney) or both. These red blood cells are destroyed, bilirubin (a break down product of haemoglobin) is produced and stored for excretion from the body in the gall bladder in bile (Davies 1997; Serjeant 2001). Sickle cell disease is a risk factor associated with the formation of pigment gall stones, with its resultant ill health (Alexander-Reindorf 1990).

Factors shown to influence the rheology of sickled cells include temperature, pH, hydration status and biochemical milieu. Apart from advice to avoid cold and dehydration, particularly during intercurrent illness and the use of prophylactic antibiotics, and vaccination in children to prevent pneumococcal infection (Fleming 1989; Hirst 2014), there is little treatment on offer until an individual is symptomatic. Treatment is supportive, with analgesia and blood transfusion. Hydroxyurea increases foetal haemoglobin (Hb F), which protects against the effects of sickle haemoglobin (Hb S), as well as prevents polymerization of the red blood cells in SCD (Nevitt 2017). The prophylactic use of hydroxyurea, in the case of recurrent painful crises and following chest syndrome, reduces hospital admissions and the need for transfusion (Nevitt 2017). Although the long-term toxicity of the drug has been a concern (Nevitt 2017), recent reviews have suggested it's long-term use over 17.5 years was safe (McGann 2011; Steinberg 2010). Its use in people with SCD with splenic sequestration is less certain (Olivieri 1998; Wang 2011), since it can cause regrowth of the spleen in older individuals (Huang 2003).

There is significant mortality from SCD (Makani 2011; Lanzkron 2013). In the lower-income areas of the world such as in parts of Africa, deaths from SCD occur in the first five years of life, with infants aged six months to one year mostly affected (Makani 2011). This is in contrast to the higher-income areas of the world with improved survival rates for children, with greater than 80% being reported (Quinn 2010). However, SCD related deaths in adults, even in the presence of comprehensive health care available in developed countries appears to be higher. In the USA, life expectancy with sickle cell anaemia was an average of 42 years for men and 48 years for women (Platt 1994) in 1994, while it was 33.4 years for men and 36.5 years for women in 2005 (Lanzkron 2013).

Families bear the majority of the burden of care for people with SCD, as there are limited social or welfare provisions available, particularly in low- and lower-middle income countries, which have the largest number of affected people (Brown 2010; Ohiaeri 2002). There is disruption of family interactions, difficulty in parental coping, psychological distress and, with repeated hospitalizations and other treatments that are required, the consumption of scarce financial resources (Brown 2010; Ohiaeri 2002).

People with SCD, as such, remain a vulnerable group and could be at risk from remedies that they may encounter (Al-Awamy 2001; Nzewi 2001). These remedies may include traditional medicines or herbal remedies, which may have true benefits or risks that might go unrecognised by the classically-trained medical fraternity.

Description of the intervention

A phytomedicine may be defined as a medicine derived from plants in their original state and standardized for use in a dosage regimen. It encompasses much of what the populations most affected would encounter in terms of plant-remedies from traditional healers. There is some documentation on a wide range of plants used in sub-Saharan Africa to treat ailments (Okigbo 2006; Verzar 1987), but there has been little in the way of systematic appraisal of their benefits in randomized controlled trials.

One of these phytomedicines is collectively known as Niprisan[®] (also known as Nicosan[®]), a freeze-dried extract of *Piper guineenses* seeds, *Pterocarpus osun* stem, *Eugenia caryophyllum* fruit and *Sorghum bicolor* leaves. Niprisan[®] has been investigated in vitro and in animal studies (Adzu 2001; Awodogan 1996; Iyamu 2002). Others are Ciklavit[®] (*Cajanus cajan* seed extract as base) and *Zanthoxylum (Fagara) zanthioides*, which are also being researched (Imaga 2013). There may well be other potential phytomedicines available for people with SCD, but their safety and efficacies will have to be scientifically evaluated.

How the intervention might work

In vitro studies with red cells from people with SCD have shown potentially clinically beneficial action of extracts of plants, including *Fagara xanthioides* (Honig 1975; Osoba 1989), *Khaya senegalensis* (Fall 1999), Griffonin and Ouabain (Larmie 1991), and *Cajanus cajan* (Akojie 1992; Ekeke 1985; Iwu 1988; Onah 2002). Unfortunately, progress has been slow and largely guided by anecdotal reports of benefit in single patients, with little in the way of larger trials. Although most in vitro work has focused on single plants, some evaluation of cocktails of plant extracts (Ohnishi 2001a; Ohnishi 2001b) has also taken place. Niprisan[®] has been shown scientifically, in in vitro studies, to delay polymerisation of

haemoglobin S, as well as reverse sickling of red blood cells when exposed to low oxygen tension (Gamaniel 1998). Gum arabic and broccoli sprout homogenate have been shown to increase Hb F production in red blood cells (Doss 2016; Kaddam 2015).

Why it is important to do this review

Phytomedicines could be important in the management of SCD, particularly in the developing world, in part because of a coming together of traditional and classical medical treatments for the benefit of a vulnerable group of people. The safety and efficacy of all phytomedicines available for people with SCD need to be scientifically evaluated. Following on from the *in vitro* studies, studies in humans have been conducted. The challenge remains to evaluate these therapies systematically, such that any true benefit and any risks to the individual with SCD are accurately reported. Randomised controlled trials (RCTs) remain the gold standard in this regard.

This is an update of previously published versions of the review (Cordeiro 2004; Oniyangi 2010; Oniyangi 2013; Oniyangi 2015).

OBJECTIVES

We aimed to assess the benefits and risks of phytomedicines compared to placebo or conventional therapy (including hydroxyurea and blood transfusion) or both in relation to symptoms and complications of all types of SCD.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs.

Types of participants

People of all ages with SCD of any genotype in any geographic setting such as: homozygous (sickle cell anaemia (HbSS)) and compound heterozygotes including SC disease (HbSC) and β -thalassaemia (S β 0/Sb+), proven by electrophoresis with family studies, deoxyribonucleic acid (DNA) tests or high-performance liquid chromatography (HPLC) as appropriate.

Types of interventions

Administration (by any mode: topical; oral; or parenteral) of phytomedicines (defined as a remedy derived directly from plants or plant material and not synthesised) compared to placebo or conventional treatment, including blood transfusion and hydroxyurea.

Types of outcome measures

Primary outcomes

1. Frequency, severity or duration of painful crises (as judged by validated pain scales, analgesia use and hospital utilisation) (change or absolute values)
2. Frequency of severe complications of SCD including sequestration crisis, acute sickle chest syndrome and leg ulcers (change or absolute values)

3. Frequency of hospital admissions from severe complications of SCD including painful crises, sequestration crises, acute sickle chest syndrome and leg ulcers (change or absolute values)

Secondary outcomes

1. Any adverse events including hepatic and renal toxicity
2. Frequency of blood transfusion (change or absolute values)
3. Level of anaemia (change or absolute values)
4. Quality of life measures (including exercise tolerance, employment and school attendance)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a search of the Group's Haemoglobinopathies Trials Register for relevant trials using the following terms: (sickle cell OR (haemoglobinopathies AND general) AND phytomedicine.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the most recent search of the Group's Haemoglobinopathies Register: 10 April 2017

We also searched the following databases and trial registries:

- AMED EBSCOHost (Allied and Complementary Medicine; 1985 to 24 August 2017);
- ISRCTN registry (www.isrctn.com; searched 26 July 2017);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 02 August 2017);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 27 July 2017).

For details of our current search strategies, please see [Appendix 1](#). Search strategies for previous versions of this review are available in [Appendix 2](#).

Searching other resources

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials; lead authors were contacted as required.

Data collection and analysis

Selection of studies

Two authors (OO, DC) independently selected the trials for inclusion in the review using pre-defined inclusion criteria as stated above that included evaluating the participants, the phytochemicals as intervention and comparisons with conventional treatment for SCD or placebo. Where there was uncertainty, the review authors contacted the trial authors for clarification. If disagreement had arisen on the suitability of a trial for inclusion in the review, the authors had planned to reach a consensus through discussion.

Data extraction and management

Prior to the 2010 update, two authors (NC, OO) had independently extracted the data and resolved differences by referring to the original trial. The process was repeated for this update by both authors (OO, DC). The authors used a structured form including participant type, demographics, geographic setting, the intervention and its control to extract the data. They extracted data for all relevant outcome measures.

Two trials were eligible for inclusion, but as these are different drug treatments and mode of action may be different, we present these separately ([Akinsulie 2005](#); [Wambebe 2001](#)).

It is currently only possible to present data at three and six months. For future updates, where possible, we plan to group outcome data into those measured at 3, 6, 12, 24 months and annually thereafter. If outcome data are recorded at other time periods, then consideration will be given to examining these as well.

For future updates of this review, we will perform an intention-to-treat analysis if data on individual participants are available for analysis.

Assessment of risk of bias in included studies

Two authors (OO, DC) independently assessed the methodological quality of each trial. In the earlier update of the review, the authors assessed the quality of included trials using the previously validated Jadad five-point scale ([Jadad 1996](#)). However, from 2010 onwards, we have used the Cochrane Risk of Bias tool to assess the risk of bias for each trial ([Higgins 2011](#)). This instrument comprises an assessment of the following domains.

1. Generation of allocation - was the allocation sequence adequately generated?
2. Concealment of allocation of assigned intervention - was allocation adequately concealed?
3. Blinding - how and who was blinded during the conduct and analysis of the trial, was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data - were incomplete outcome data adequately addressed?
5. Selective reporting - selective availability of data for outcomes (time points, subgroups or analyses); are reports of the study free of suggestion of selective outcome reporting?
6. Other potential sources of bias - was the study apparently free of other problems that could put it at a high risk of bias?

We have assessed these criteria as having either a low, unclear or high risk of bias. If the study reports insufficient detail of what happened, the judgement will usually be 'unclear' risk of bias. We recorded these judgements in the Review Manager (RevMan) software in a risk of bias table and generated a risk of bias summary figure ([Figure 1](#)) to determine the overall risk of bias of the included trial ([RevMan 2014](#)).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green, yellow and red refer to low, unclear and high risk of bias respectively.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Clinicians	Blinding (performance bias and detection bias): Participants	Blinding (performance bias and detection bias): Outcome assessors	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Akinsulie 2005	+	+	-	+	+	?	?	-
Wambebe 2001	?	+	+	+	?	?	?	?

Where there was uncertainty, the review authors contacted the trial authors for clarification. If disagreement had arisen on the suitability of a trial for inclusion in the review, we had planned to reach a consensus through discussion.

Measures of treatment effect

For continuous variables presented, we calculated a mean difference (MD) or standardized mean difference (SMD) and 95% confidence interval (CI) for the included trial when appropriate.

For future updates, when binary variables are included in the review, we will calculate an odds ratio (OR) with 95% CIs for individual studies. All similar studies will be pooled using an OR and 95% CIs.

We will also perform an intention-to-treat analysis if data on individual participants are available for analysis.

Unit of analysis issues

We anticipated cross-over trials may be included. Methods for meta-analysing cross-over trials are discussed by Elbourne (Elbourne 2002). The methods discussed rely on the data that are reported within the primary paper. We aimed to use the most appropriate method available to analyse these data. Where possible, we entered the data for the outcomes of the trial into the analysis for first-period data. It is possible that an intervention will have a carry-over effect in which case we will not report the data from the second period (after cross-over). For updates, we plan to use the most appropriate method to analyse cross-over data that is available in RevMan (RevMan 2014).

Dealing with missing data

We contacted the primary authors of both included trials of the review in December 2009 and requested individual patient data which we hoped to include in a future update of the review. Unfortunately we have been unable to obtain any more information.

Assessment of heterogeneity

When more trials are included within the review (minimum of four), we plan to test for heterogeneity using a standard χ^2 test. We will also use the I^2 test to assess the impact of heterogeneity on the meta-analysis (Higgins 2003). We will quantify heterogeneity as follows:

- 0% to 40%: not important or low;
- 30% to 60%: moderate;
- 50% to 90%: substantial; and
- 75% to 100%: considerable heterogeneity (Deeks 2011).

These analyses were not possible in this update as we were only able to include two trials for analysis.

Assessment of reporting biases

We plan to examine publication bias using meta-regression and assess selective reporting as detailed above.

Data synthesis

For future updates of the review and when more trials are included, where we find heterogeneity to be statistically significant, we will use a random-effects model; where we find it not to be statistically significant, we will use a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

For future updates of the review and when more trials are included, we will use meta-regression to look for associations between key measures of trial quality and treatment effect size, and to examine for other sources of heterogeneity.

We will assess possible sources of heterogeneity by subgroup analysis. We will attempt subgroup analyses if there are sufficient numbers of adequately-sized trials, and stratify according to sickle status (e.g. SS or SC), severity of disease (e.g. SS versus SC), age (children versus adults) and geographic setting.

Sensitivity analysis

We will also perform sensitivity analyses based on the risk of bias (i.e. those with an unclear or high risk of bias versus those with a low risk of bias in relation to generation of the allocation sequence) of the trials.

Summary of findings tables and quality of the evidence

In a post hoc change, the authors have presented two summary of findings tables; one for each comparison (Summary of findings for the main comparison; Summary of findings 2).

All seven outcomes (see Types of outcome measures) are presented at the latest time point recorded (i.e. six months) in the Summary of Findings tables. For clarity in the tables, adverse events are not presented according to the specific events as outlined in Effects of interventions; instead we have inserted a general statement about

the summary of findings for these outcomes and the evidence is graded based on all of the specific events.

The authors determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence or imprecision of results (or both). They downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

Results of the search

The search strategy identified reports of five trials, of which two (including a total of 182 participants) were eligible for inclusion (Akinsulie 2005; Wambebe 2001) and three were excluded (Doss 2016; Kaddam 2015; Panigrahi 1997).

Included studies

Niprisan® versus placebo or conventional treatment

Trial design

This was a Phase IIB (pivotal) clinical trial conducted in Nigeria by the National Institute for Pharmaceutical Research and Development (NIPRD) that compared the safety and efficacy of a phytomedicine derived from plants indigenous to Nigeria (Niprisan®) in people with SCD (Wambebe 2001). The trial was double-blind and randomised, with concealment of allocation. It was of cross-over design, with each arm randomised to receive placebo or Niprisan® for a total of six months. No washout period is clearly described. In only one of the references is such a period of one month mentioned. Although a period of one month is mentioned in the article in *Current Therapeutic Research*, it is not clear how this period of time was decided upon (Wambebe 2001). The protocol was approved by the National Agency for Food and Drug Administration and Control (NAFDAC) of Nigeria and the Ethical Committee of the NIPRD. Written informed consent was obtained from the adult participants, and the caregivers and parents of younger children.

Participants

This trial included 82 participants, although availability of outcome data varied from 52 to 82 participants (Wambebe 2001). The trial included people of all ages (actual age range 2 to 42 years old, but mainly adolescents with the majority in each group being students) with HbSS, confirmed by haemoglobin electrophoresis. Participants were known to have moderate to severe recurrent episodes of crises, having experienced three or more painful or vaso-occlusive crises in the previous year. These crises (which may have included episodes of acute chest syndrome, splenic or hepatic sequestration or priapism) were defined as an acute painful event requiring treatment with:

1. parenteral narcotics;
2. or equianalgesic dose of oral narcotic;
3. or parenteral non-steroidal anti-inflammatory drugs;
4. or equianalgesic oral dose of non-steroidal anti-inflammatory drugs.

The trial report outlined conditions for severe crises, but failed to mention how mild to moderate crises were identified ([Wambebe 2001](#)).

Potential participants were excluded if they:

1. had clinical features of AIDS;
2. had hepatitis;
3. were pregnant or lactating;
4. had a history of hypersensitivity (more information is required on hypersensitivity and authors have been contacted);
5. were unwilling or unable to follow instructions regarding treatment.

The treatment groups were similar in terms of age and sex at the outset.

Interventions

The active formulation, Niprisan[®], derived from plants indigenous to Nigeria, was previously assessed in both in vitro and in animal studies ([Adzu 2001](#); [Awodogan 1996](#); [Gamaniel 1998](#); [Iyamu 2002](#)). Participants were randomised to receive either Niprisan[®], a freeze-dried extract of *Piper guineenses* seeds, *Pterocarpus osun* stem, *Eugenia caryophyllum* fruit and *Sorghum bicolor* leaves, at a single daily dose of 12 mg/kg or placebo. Neither the reasons or calculations for this dose; nor the aspect of the composition of the plant extracts used to calculate the dosage from the active ingredients were stated. Niprisan[®] and placebo were presented in identical capsule form to be taken orally for six months. Thereafter, participants switched study arms to receive the other drug (i.e. placebo or Niprisan[®]) in the cross over design of the trial. No washout period was clearly described as mentioned above. In addition, all participants received malaria prophylaxis and folic acid. Methods to check for adherence to medications prescribed were not stated.

Outcomes

Outcomes were recorded in the form of self-assessment using a health diary, by all participants (both adults and children). This was not a previously validated instrument. A period of four months prior to the start of the trial served to establish training in the use of the diary. The assessment was then continued for 12 months, with six months dedicated to each stage of the cross-over trial. The health diary recorded 36 symptoms and questions and was graded for severity as follows: none (0); mild (1); moderate (2); severe (3). It was not stated how the quality of life measures were assessed and we have contacted trial authors regarding this.

Clinical assessments were based on the health diary recording symptoms and other indicators of ill health and in particular the degree and frequency of pain. Clinicians also made clinical assessments on participants on a weekly basis at the participants' homes using the same criteria to assess pain as the volunteers; and on a monthly basis during participants' attendance at the NIPRD clinic, where additionally blood samples were analysed as detailed below. It was not stated how pain severity was ascertained in the young children who were included in the trial.

Laboratory assessments consisted of a pre-trial blood test from each participant and then monthly blood tests throughout the trial period. Baseline haemoglobin levels (to ascertain the degree

of anaemia) were recorded as well as levels of liver enzymes (to assess liver function): alanine amino-transferase (ALT); alkaline phosphatase; and gamma glutamine transferase (GGT). Renal function was determined with serum creatinine and blood urea nitrogen (BUN). Nutritional status and metabolic status were assessed by concentrations of: total protein; albumin; total calcium; fasting total cholesterol; fasting triglyceride; fasting blood glucose; and uric acid. All analyses were repeated at cross-over to establish a baseline at this time and at the end of the trial.

Ciklavit[®] versus placebo or conventional treatment

Trial design

This trial was a prospective randomised placebo-controlled single-blind intervention trial comparing the safety and efficacy of a phytomedicine derived from plants indigenous to Nigeria (Ciklavit[®], an extract of *Cajanus cajan*) to placebo in people with SCD ([Akinsulie 2005](#)). Although single blind, concealment of allocation was employed. We contacted trial authors and details of the process are described in the section on the [Risk of bias in included studies](#).

Informed consent was obtained from guardians and ethical clearance granted before the commencement of the trial, by the ethics committee of the Lagos University Teaching Hospital, Nigeria.

Participants

The initial recruitment of 100 (50 in each group) drew participants from the Sick Cell clinic at Lagos University Teaching Hospital. This trial included children with sickle cell anaemia (HbSS), between the ages of 1 and 15 years, with HbSS status confirmed by haemoglobin electrophoresis.

Exclusions applied to children:

1. with febrile illness in the preceding two weeks;
2. who had participated in any other drug trial in the preceding six months; or
3. who had evidence of organ failure.

Routine medications (folic acid and anti-malarials) were not seen as criteria for exclusion.

Interventions

Participants were randomised to receive either Ciklavit[®], an extract of *Cajanus cajan*, an edible local bean, or placebo. A 10 ml aliquot of the extract contained protein (49 mg) with phenylalanine as its major component. The anti-sickling property of the *Cajanus cajan* extract has been attributed to this amino acid. Zinc (400 ug) and ascorbic acid (50 mg) were added as preservatives. The placebo contained zinc (400 ug) and ascorbic acid (50 mg). Children below the age of five years received 10 mL twice daily of active product or placebo, and those over the age of five years received 20 mL twice daily, as per manufacturer's instructions. Both groups of children were placed in the same treatment arm. It was not stated how the manufacturers arrived at this dosage.

Outcomes

Data were collected in several steps. Individuals were given a daily assessment form for documentation of painful episodes and were seen monthly for six months. It was not stated if there was a period

of training in the use of the self assessment forms prior to the onset of the trial. We have contacted authors and requested this information.

There was also a standardised questionnaire employed with a complete physical assessment at the outset, three months and six months. This included laboratory assessments comprising blood tests for measurement of packed cell volume (PCV) (a measure of anaemia or blood level), serum bilirubin (a measure of the break down products of destroyed red blood cells and liver function), and urea and creatinine (measures of kidney functions) and urine analysis.

Excluded studies

Three trials were excluded, although prospective, these were neither randomised or controlled (or both) or quasi randomised or controlled (or both), as stated in the [Characteristics of excluded studies](#) table (Doss 2016; Kaddam 2015; Panigrahi 1997).

Risk of bias in included studies

The risk of bias of the included trials was assessed using the Cochrane risk of bias tool (Higgins 2011). Please refer to [Figure 1](#).

Niprisan® versus placebo or conventional treatment

Allocation

Generation of allocation sequence

This study was described as randomised. The trial authors report that participants were randomised into two treatment groups by 'simple random sampling' (Wambebe 2001). The process of randomisation was not stated and we have been unable to obtain further information on this from the authors. We judged this process as 'unclear'.

Concealment of allocation sequence

The participants and trial authors could not foresee the assignment of each participant as the allocation was done centrally by a third party not directly involved with the trial (Wambebe 2001). We judged this process as having a low risk of bias.

Blinding

This study was described as double-blind (Wambebe 2001). This double blinding was achieved for participants and clinicians by using an identical capsule as placebo, which was of the same colour and smell as the active formulation and was appropriate. Knowledge of the intervention was adequately concealed during the trial from both participants and investigators. We judge this process to have a low risk of bias.

Incomplete outcome data

Withdrawals and dropouts were enumerated in the body of the report and the numbers for each group given. The reasons given for dropouts were mainly due to incompleteness of health diary cards, although one participant was lost to follow-up, due to relocation from the study site. No information on the demographic composition of those who withdrew or dropped out was given and how this compared with the rest of the trial group. Therefore, bias cannot be discounted in the final analysis. There is no information on any additional measures undertaken to contact

those participants lost to follow-up. We have contacted the trial authors to obtain individual patient data.

The trial also did not state whether an intention-to-treat approach was used (Wambebe 2001).

We judge this process as 'unclear' as we would need further information from the trial authors to adequately address this.

Selective outcome reporting

The study objectives were listed as assessing the efficacy and safety of the intervention (Wambebe 2001). The study outcomes were not explicitly pre-specified, although the measures to obtain the reported outcomes were described in detail.

We judge this as 'unclear' as we would need further information from the authors to adequately address this.

Other potential sources of bias

The study authors have not stated any potential sources of bias. However, we note that a washout period was not carried out as part of the design of the cross-over trial, and this has limited the interpretation of the results of the second six months of the trial. We have contacted the authors for more details regarding this period. Furthermore, self assessments for data collection may introduce bias as this is a subjective assessment and there was no correlation of clinicians' assessment and self assessments even though the authors mentioned that clinician data were compared to the participant data. Finally, most of the study participants were adolescents, although the age range was 2 to 42 years. This could affect the reporting of the primary outcomes such as the frequency of severe painful crises that are influenced by age. We therefore judge this risk of bias as 'unclear' as we need further information from the trial authors to adequately address this issue.

Ciklavit® versus placebo or conventional treatment

Allocation

Generation of allocation sequence

This was described as using block randomisation (Akinsulie 2005). The generation of random sequence was by shuffling sequentially numbered envelopes in blocks of ten. This was repeated when the block was exhausted. The allocation sequence was adequately generated and we judge this as having a low risk of bias.

Concealment of allocation sequence

Totally opaque brown envelopes of the same size were used (Akinsulie 2005). The envelopes were held by the clinic nurse who allocated the treatment once the inclusion criteria had been met. The nurse was not one of the trial investigators. Once one of the investigators saw an individual eligible for inclusion in the trial, after obtaining informed consent, the individual was sent to the clinic nurse, in another room, who held the envelopes. She selected the first randomly assigned envelope containing either the test product or placebo, which was unknown to either the participant or the nurse. For the subsequent eligible participant, the next envelope was selected until the block envelope was exhausted and the process was repeated for the next block. The participants and trial authors could not foresee the assignment of each participant as the allocation was done by central allocation by a third party not

directly involved with the trial. We judge this process as having a low risk of bias.

Blinding

The trial was single blind because the manufacturer could not conceal the physical appearance of the products adequately, at least for the clinicians involved in the trial at the time. However, the participants were blinded to the preparations, and those who carried out the laboratory analyses were also blinded to both the participants and the preparations. It should be stated that the products were in liquid form. We judge this process as having a high risk of bias as the knowledge of the allocated intervention was not concealed from the clinicians or the participants (Akinsulie 2005).

Incomplete outcome data

Withdrawals and dropouts were enumerated in the report and the numbers for each group given, as well as the demographic makeup of groups as a final result of this. The trial did not state whether an intention-to-treat approach was used. (Akinsulie 2005). We judged there to be an 'unclear' risk of bias for this criteria, as more information is required on the intention-to-treat analysis.

Selective outcome reporting

The study objectives were listed as determining the changes (if any) in the clinical and laboratory features of SCD in participants receiving the *Cajanus cajan* extract (Akinsulie 2005). The study outcomes were not explicitly pre-specified, although the data to be collected were stated. We judge the risk of bias for this criteria to be 'unclear' as we would need further information from the authors to adequately address this.

Other potential sources of bias

The study authors have not stated any potential sources of bias. However, we note that self assessments for data collection may introduce bias as this is a subjective assessment and there was no correlation of clinicians' assessment and self assessments. The adult caregivers would have assessed the younger children. Recall of events for up to six months before the study was compared to events occurring during the study. Also, analysis of data was done within groups rather than across groups. We judge the risk of bias from this as 'unclear' as we would need further information from the trial authors to adequately address this issue.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings - Niprisan® versus placebo for sickle cell disease](#); [Summary of findings 2 Summary of findings - Ciklavit® versus placebo for sickle cell disease](#)

Due to the reasons highlighted in the 'Unit of analysis issues' section, we have only presented data for the first six-month period of the Wambebe trial (first period data). For several secondary outcomes we have also analysed these data (Wambebe 2001). We have contacted the authors and requested further data for inclusion in future updates of this review (December 2009) (Wambebe 2001). Unfortunately, to date no reply has been obtained. For those outcomes where the data were reported as being skewed, ideally we would have reported the medians and interquartile ranges. However, only the means and the standard deviations (SDs) were presented in the primary papers and these are reported within the

review. Confidence intervals are presented below if available. Given these factors, the results should be interpreted with caution.

Notwithstanding our reservations of the Akinsulie trial being a single-blind trial (Akinsulie 2005), we feel that the authors took all precautions to conceal the allocation. Therefore, we also report on their preliminary data below.

Niprisan® versus placebo or conventional treatment

One trial (82 participants) was eligible for inclusion (Wambebe 2001).

Primary outcomes

1. Frequency, severity or duration of painful crises (as judged by pain scales, analgesia use and hospital utilisation)

Data from health diaries were available from 70 participants (Wambebe 2001). Participants reported mild, moderate and severe pain using a scale from zero to three, as described above. Results are reported for mild or moderate pain and severe pain separately. In the first six months, the treatment group (n = 34) showed a significant difference relative to the placebo group (n = 36) for severe pain episodes occurring with a mean (SD) of 7.9 (8.4) times, compared to 21.1 (32.9) times in the placebo group (low-quality evidence). Given that data were skewed (and therefore cannot be analysed in RevMan), analysis of these data was undertaken by the trial authors using a non-parametric method (RevMan 2014). No statistically significant difference was noted between groups as regards mild or moderate pain in the first six-month period.

2. Frequency of severe complications of SCD including sequestration crises, acute sickle chest syndrome and leg ulcer

Summary statistics were provided for the frequency of reported crises, by treatment group and trial period per month (Wambebe 2001). This was based on completed health diaries from 70 participants. In the first six months, no statistically significant difference by distribution was found between the treatment (n = 34) and placebo (n = 36) groups (low-quality evidence). No separate information is provided on sequestration crises, sickle chest or leg ulcer.

3. Frequency of hospital admissions from severe complications of SCD including sequestration crises, acute sickle chest syndrome and leg ulcer

The difference between groups, before cross-over in relation to frequency of hospital admissions per month was not significant (low-quality evidence) (Wambebe 2001).

Secondary outcomes

1. Any adverse events including hepatic and renal toxicity

Two participants on Niprisan® developed non-itching macular rashes three to four days after starting treatment, which disappeared a few days later (Wambebe 2001). Six participants on Niprisan® developed headache compared to two on placebo. Laboratory results were reported for a total of 52 participants (27 in the Niprisan® group and 25 in the placebo group). One participant in the Niprisan® group had altered liver function at the start of the trial, but this did not deteriorate or change over the trial period. Tests showed no significant difference in liver or kidney (renal) function between the arm receiving Niprisan® (the active formulation) or the placebo arm at the end of the first six months. There was

also no change relative to baseline values recorded four months prior to administration of the formulation or placebo. After the first treatment period at six months, the differences in the mean activities of all the measured liver enzymes were not statistically significant. The mean difference for ALT was -1.00 IU (95%CI -5.74 to 3.74); for AST, 7.00 IU (95% CI -6.28 to 20.28); for ALP, 2.00 IU (95% CI -5.93 to 9.93); and for GGT, -3.00 IU (95% CI -8.42 to 2.42). There were also no significant changes in levels of serum creatinine, MD 1.00 µmol/L (95% CI -10.95 to 12.95) or of BUN, MD 0.30 mmol/l (95% CI -0.25 to 0.85) (low-quality evidence) ([Analysis 1.1](#)).

2. Frequency of blood transfusion

This outcome was not reported ([Wambebe 2001](#)).

3. Level of anaemia

Haemoglobin level was reported for 52 participants (27 participants receiving Niprisan® and 25 receiving placebo in the first six months prior to cross-over) ([Wambebe 2001](#)). Haemoglobin was reported as a mean (SD) in g/dL for each group relative to baseline within groups, as well as between groups. At six months the mean difference (MD) of haemoglobin concentration was 0.30 g/dL (95% CI -1.83 to 2.43), which was not statistically significant (low-quality evidence) ([Analysis 1.2](#)).

4. Quality of life measures (including exercise tolerance, employment and school attendance)

The comparability of the two groups was assessed pre-trial using the health diary, completed by study participants. There was no mention of any differences in this assessment tool (health diaries) for the adults and children. Given that these data were skewed, analysis was performed within the primary paper using a non-parametric method ([Wambebe 2001](#)). There were no significant differences between groups at the outset. At six months, 70 participants had completed health records, and participants reported health being below average in the active treatment group (n = 34), with a mean (SD) of 12.2 (11.6) times, compared to the placebo group (n = 36) with a mean (SD) of 31.3 (31.4) times (very low-quality evidence). This difference was not statistically significant.

Summary statistics were provided for absenteeism from work or school, based on results available for 70 participants ([Wambebe 2001](#)). The distribution is skewed for these results, so data have not been presented at this stage, as only summary statistics are available. In the first six months, in the between group analysis, there was no significant difference between the active treatment (n = 34) and placebo (n = 36) groups, as regards absenteeism from work or school.

Ciklavit® versus placebo or conventional treatment

One trial (100 participants) was eligible for inclusion ([Akinsulie 2005](#)).

The authors did not report effect across groups (treatment versus control) at six months ([Akinsulie 2005](#)). Rather, they reported effects within groups.

Primary outcomes

1. Frequency, severity or duration of painful crises (as judged by pain scales, analgesia use and hospital utilisation)

They reported there were 207 episodes of painful crises (mean 4.4, SD 10.3) before the study, and 191 episodes (mean 4.2, SD 4.2) during the study among the intervention group; and 109 episodes (mean 2.6, SD 50) before the study and 164 episodes (mean 3.9, SD 4.3) during the study among the control group (low-quality evidence). Given the skewed nature of these data, we were unable to enter these data into the 'Data and analyses' section.

2. Frequency of severe complications of SCD including sequestration crises, acute sickle chest syndrome and leg ulcer

This outcome was not reported ([Akinsulie 2005](#)).

3. Frequency of hospital admissions from severe complications of SCD including sequestration crises, acute sickle chest syndrome and leg ulcer

This outcome was not reported ([Akinsulie 2005](#)).

Secondary outcomes

1. Any adverse events including hepatic and renal toxicity

The trial reports that there was no significant change in level of bilirubin, urea or creatinine during the study, but figures were not provided ([Akinsulie 2005](#)). There were no significant differences between the groups regarding the following adverse events. Vomiting occurred in one participant in each group. The authors reported tiredness (one participant) and abdominal distention (one participant) in the study group, and peri-orbital swelling (one participant), diarrhoea (one participant), and itching of the eyes (one participant) in the control group (low-quality evidence). These were reported as being transient events. For full summary statistics, please refer to [Analysis 2.1](#).

2. Frequency of blood transfusion

This outcome was not reported ([Akinsulie 2005](#)).

3. Level of anaemia

Packed cell volume was reported ([Akinsulie 2005](#)). The across group comparisons are not reported in the original trial report, but on entering data presented into the RevMan analysis we showed no significant difference between treatment and control groups at three months, MD -1.52 (95% CI -3.49 to 0.45); and six months, MD -1.54 (95% CI -3.16 to 0.08) (low-quality evidence) ([Analysis 2.2](#)). This suggested a fall in PCV in the treatment group, although formal testing for trend for this outcome was not performed in our analysis.

4. Quality of life measures (including exercise tolerance, employment and school attendance)

This outcome was not reported ([Akinsulie 2005](#)).

DISCUSSION

The Niprisan® trial was the first randomised controlled trial to report on the use of phytomedicines in sickle cell disease (SCD) ([Wambebe 2001](#)). The active formulation, Niprisan®, derived from plants indigenous to Nigeria, was previously assessed in vitro and in animal studies ([Adzu 2001](#); [Awodogan 1996](#); [Gamaniet 1998](#); [Iyamu 2002](#)). Further multicentre studies in humans are awaited. In this trial ([Wambebe 2001](#)), the results from several outcomes were

not normally distributed and it was therefore not appropriate to analyse these in RevMan (RevMan 2014). Therefore, only the first six months of results are reported within this review.

The Ciklavit® trial was conducted as a single-blind randomised placebo-controlled trial in children with SCD (Akinsulie 2005). However, some limitations came to light in the reporting of the results. Most comparisons were made within groups rather than across groups. Different age groups receiving different doses of the medications were analysed within the same treatment arms, although ideally they should have been analysed separately. This may have added a confounder to the results. We recognize that the authors chose this approach as the data set were non-parametric. We were unable to compare across groups within the RevMan analyses given the skewed nature of the data (RevMan 2014). Our analyses aimed to compare data across intervention arms, rather than within intervention arms, and from these, we reached our conclusions regarding the trial.

The numbers examined in both trials (Akinsulie 2005; Wambebe 2001) were small and although no power calculations were stated in the original papers, it is likely that the trials were too under-powered to detect any but the largest effects. Moreover, as multiple comparisons are made, results of borderline significance are to be interpreted cautiously.

The main effect reported in the trials was a reduction in severe pain episodes in those receiving the active formulations - Niprisan® and Ciklavit®. This was done by self assessment, which is subjective; and furthermore there may have been difficulty in interpreting pain for younger children. The subjectivity of pain assessments in very young children by others limits its interpretation. In the Niprisan® trial, a clear definition of the pain scale used and health perception scales were not given, nor were there any data presented relating to their reliability or validity. In the Ciklavit® trial, baseline frequency of painful crises was measured by verbal recall across both groups. This may not have been accurate or truly representative of the events particularly in the younger children where there may have been difficulty in interpreting pain by their care givers and parents. Therefore caution is advised in interpreting results comparing these baseline events to those occurring during the trial.

Both trials (Wambebe 2001, Akinsulie 2005) included children and adolescents, with limited number of adults. There may well be a benefit of the formulations to other age groups and it is hoped that more research in the form of larger trials can address this.

The Niprisan® formulation seems safe with no serious adverse symptoms or derangement of liver or kidney function in the participants. However, a potential worrying adverse event of Ciklavit® may be the effect on anaemia (as measured by decrease in PCV), although the within-group differences were not significant for the treatment group. The authors have suggested that this may be due to an ameliorating effect of the Ciklavit® on the mechanism by which zinc and ascorbic acid, present in both active drug and placebo cause a rise in PCV. This should be reported on in future trials.

Finally, both trials only looked at people with sickle cell anaemia (HbSS) and not other forms of SCD. It is hoped that future trials will address this issue.

Summary of main results

We identified two trials that compared the effectiveness of phytomedicines (Niprisan® and Ciklavit®) with placebo in SCD.

Niprisan®

The Niprisan® trial was the first randomised controlled trial to report on the use of phytomedicines in SCD (Wambebe 2001).

The main effect reported in this trial was a significant reduction in severe pain episodes in those receiving the active formulation. This was not so in those with mild or moderate pain episodes.

Summary statistics were provided for the frequency of all reported painful crises. However, as no separate information was provided on sequestration crises, sickle chest or leg ulcer, we are therefore unable to report on the effect of the active formulation on these complications.

Comparing the results between the two treatment groups, as well as within the intervention arm of the trial after six months, no significant difference was reported in the following outcomes: hospital admissions; haemoglobin levels; liver and kidney function tests or quality of life measures.

Blood transfusion rates were not reported on.

Ciklavit®

The main effect reported in the Ciklavit® trial (Akinsulie 2005) was a reduction in the number of painful episodes in the intervention arm (from baseline to six months), which was not so documented in the placebo arm. However, comparisons between the control and intervention groups were not carried out given the skewed nature of the data.

Comparing the results within the intervention arm of the trial after six months, no significant difference was reported in the following outcomes: PCV (although a reduction was observed); urea; creatinine; or bilirubin levels; as well as clinical adverse events; and liver and kidney function tests.

Frequency of severe complications of SCD including sequestration crises, acute sickle chest syndrome, leg ulcers, hospital admissions, blood transfusion rates and quality of life measures were not reported on in this trial.

Overall completeness and applicability of evidence

This review aimed to assess the benefits and risks of phytomedicines compared to placebo or conventional therapy in all forms of SCD. We identified two randomised controlled trials that compared the efficacy of phytomedicines to placebo in people with sickle cell anaemia. The included trials had individually assessed different outcomes of the review. However, collectively these trials had addressed most of the questions raised in the outcomes of the review, albeit with varying results. The evidence generated from both trials are therefore relevant to answer some of the review questions, although there are certain limitations in the conduct of the trials that may affect the evidence generated.

Of the different types of crises that occur in SCD, only the painful crises were evaluated by both trials. Neither the effects of phytomedicines on the frequency of severe complications of SCD

including sequestration crisis, acute sickle chest syndrome and leg ulcers, nor on the blood transfusion rates were evaluated.

Both trials were conducted in areas of malaria endemicity, and as such, all participants received malaria prophylaxis as well as folic acid supplementation. Malaria is associated with precipitating painful crises and anaemia in SCD (Konotey-Ahulu 1971) and primary malaria prevention has been found to reduce these events (Oniyangi 2006). If all the trial participants adhere to malaria prophylaxis, this is unlikely to confound results. However, we could not ascertain participants' adherence to a set dosing regimen of malaria prophylaxis. This may be relevant to the interpretation of observed difference in effects reported in the trials.

The participants in the Niprisan® trial were unpaid volunteers, although participants received transportation costs to encourage follow-up. As volunteers, they may not be truly representative of the general SCD population. In general it has been found that volunteers may exhibit outcomes different from non-volunteers, e.g. they may be healthier (MUSC 2001). They also may be more interested in the particular topic or have stronger opinions on that topic, which in turn may lead them to favour the treatment. The groups were reported as randomised even though the mechanism of randomisation was not stated. The blinding processes were deemed appropriate and the participants satisfied the inclusion criteria of the trial. Hence, these factors should not influence any potential differences in effect within the trial. However, the fact that the majority of the participants were adolescents may affect the reporting of some outcomes such as frequency of severe painful crises, which may be affected by age.

Furthermore, these trials had assessed only participants with sickle cell anaemia, and as such the results of the review are not applicable to people with other sickle cell genotypes. It is hoped that future trials will address this observed deficit.

Quality of the evidence

We judged the quality of the evidence from this review to be of low to very-low quality, depending on the outcome measured.

Low-quality evidence implies we can have some confidence in the result, but further research evidence would be helpful and is likely to change the estimate. Very low-quality evidence implies we are very uncertain about the estimate.

The quality of evidence was downgraded under 'limitations in design and implementation of studies, and 'indirectness of evidence'.

Limitations in design and implementation of studies refers to the methodological quality of the included studies. This was flawed in the generation of allocation sequence used, which was not well described in the Niprisan® trial, although stated as simple randomisation. There was inadequate blinding of clinicians to the formulation used in the Ciklaviv® trial which was a potential source of bias. Furthermore, it was not stated in both trials if an intention-to-treat analysis was used.

Indirectness of evidence is an assessment of how well the evidence matches the question being asked (population, intervention, control, outcome). The participants in both trials were people with

sickle cell anaemia, and therefore, the evidence generated may not be applicable to people with other forms of SCD.

Potential biases in the review process

The review included two trials assessing the usefulness of phytomedicines for managing SCD (Akinsulie 2005; Wambebe 2001). More recent studies were found after an extensive search strategy but these were not included in the review because they did not satisfy the inclusion criteria (randomised or quasi-randomised controlled trials). Three studies were excluded from the review which assessed other phytomedicines for managing sickle cell anaemia as they were not randomised control trials (Doss 2016; Kaddam 2015; Panigrahi 1997).

The included trials were independently assessed by the authors for methodological accuracy and also for risk of bias using the Cochrane risk of bias tool (Higgins 2003). The evidence from the studies were judged as low quality evidence primarily due to poor generalisability to persons with sickle cell genotypes, unclear randomisation methods, lack of blinding, self reported data and the lack of clarity on if an intention-to-treat analysis was done.

Finally, there were limitations in the interpretation of data from the trials. Only data of the first six months of the Niprisan® trial was included for analysis, because it was a cross-over trial and no clear description of a washout period was documented (Wambebe 2001). Data from the Ciklaviv® trial reported within-group analysis, which is not as objective as an across-group analysis (Akinsulie 2005). We were unable to compare across intervention groups given the skewed nature of the Ciklaviv® trial data; and from these, inferences were made regarding the trial.

Agreements and disagreements with other studies or reviews

The authors were not able to locate any other systematic review or meta-analysis which addressed the use of phytomedicines for managing SCD. However, there was one study on treatment of sickle cell disorders by ayurvedic medicine (Panigrahi 1997). Furthermore, two additional studies were assessed subsequent to the last update of this review (Doss 2016; Kaddam 2015). These studies highlighted the use of broccoli sprout homogenate (Doss 2016) and Gum arabic (Kaddam 2015) as phytomedicines,

The mechanism of action of these herbal preparations differed from the anti-sickling properties for Niprisan® and Ciklaviv® reported in the trials included in this review. These two substances, broccoli sprout homogenate and Gum arabic, cited in the more recent studies (Doss 2016; Kaddam 2015) were reported to increase foetal haemoglobin (Hb F) in persons with SCD. The mechanism of the third phytomedicine, the ayurvedic medicine (Panigrahi 1997) was not stated, but was noted to improve pain and haemoglobin levels, although in conjunction with folic acid administration, which is a haematinic (blood builder).

These studies cited above differed from the present review in neither being randomised nor controlled trials. They can therefore not be compared to the trials included in this Cochrane Review.

AUTHORS' CONCLUSIONS

Implications for practice

Niprisan® and Ciklavit®, both phytomedicines for SCD, have been the subject of analysis in randomised controlled trials ([Akinsulie 2005](#); [Wambebe 2001](#)). However, both trials had small sample sizes and there was an absence of power calculations which limits the interpretation of their results. It is therefore likely that the trials were too under-powered to detect any but the largest effects. Moreover, as multiple comparisons are made, results of borderline significance are to be interpreted cautiously.

While Niprisan® appeared to be safe and effective in reducing severe painful crises over a six-month follow-up period, further trials are required to assess its role in the management of people with SCD. There is still no report of the planned multi-centre follow-up trials on this drug which would have provided additional information. No conclusions can be made at present regarding the efficacy of Ciklavit®.

Based on the published results for Niprisan® and in view of the limitations in data collection and analysis of both trials, phytomedicines may have a potential beneficial effect in reducing painful crises in SCD. This needs to be further validated in future studies. More trials are required on the safety and efficacy of phytomedicines in the management of SCD.

Therefore, at this stage, no recommendations can be made regarding the use of either of these medications in SCD.

Implications for research

Trials investigating the use of phytomedicines in SCD need to be well-designed, with improved measures to validate self-

assessment data. They should also be adequately powered with appropriate methods for analysing data. One of the difficulties in interpreting the results of the trials included in this review, is the lack of detail provided for assessments of pain and quality of life measures; and their validation. There is clearly a need for standard measures to be developed. Similarly, more research is needed to clarify the benefits of both drugs in SCD, particularly with the lack of benefit noted in the across-groups analysis of Ciklavit®. The potential for an adverse effect of Ciklavit® on anaemia needs to be clarified. For cross-over trials, an adequate washout period between treatment arms is required. Future research will need to address:

1. long-term effects (i.e. benefit and toxicity) of phytomedicines;
2. impact on other forms of SCD;
3. impact and safety profile in children and adults with SCD;
4. impact on use of transfusions in SCD;
5. impact on painful and sequestration crises, chest syndrome and other complications including leg ulcers;
6. impact on hospital admissions from complications of SCD;
7. approaches or measures to validate for data collected for the self assessments.

ACKNOWLEDGEMENTS

Professor Sally Davies for her help and support in organising this protocol.

Professor Rosalind Smyth for supervising the systematic review process.

Dr Nuno Cordeiro for the significant input into the development of the protocol and the initial review and first update.

Dr Temiye EO, contact author for the Akinsulie trial for clarifying issues related to the trial ([Akinsulie 2005](#)).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akinsulie 2005

Methods	Randomised, single-blind, placebo-controlled trial. Single centre in Nigeria.
Participants	100 participants, of which 50 received active formulation and 50 received placebo. These consisted of children between the ages of 1 and 15 years, with HbSS status confirmed by haemoglobin electrophoresis.
Interventions	< 5 years: 10 mL twice-daily of Ciklavit® or placebo.

Akinsulie 2005 (Continued)

> 5 years: 20 mL twice-daily of Ciklavit® or placebo.

Outcomes	Painful crises, PCV as a measure of anaemia.
Notes	There was no indication in the trial report that the clinical researchers were not the clinicians observing the participants during the study. Also, neither the clinical researchers nor the participants were sufficiently blinded to the physical properties of the intervention and this may have led to biased ascertainment and adjudication of outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>This was described as randomised. Details of randomisation provided by the trial authors were as follows: block randomisation was employed. The generation of random sequence was by shuffling the concealed allocation (in an opaque envelope in blocks of tens, which were shuffled and then numbered sequentially. This was repeated when the block was exhausted.</p> <p>Once one of the investigators saw an individual eligible for inclusion in the trial, after obtaining informed consent, the individual was sent to the clinic nurse, in another room, who held the envelopes. She selected the first randomly assigned envelope containing either the test product or placebo, which was unknown to either the participant or the nurse. For the subsequent eligible participant, the next envelope was selected until the block envelope was exhausted and the process was repeated for the next block.</p>
Allocation concealment (selection bias)	Low risk	The envelopes were totally opaque brown envelopes of the same size. A member of staff who was not part of the study team (a nurse) was asked to pick a randomly assigned envelope, which contained the preparation to be given to the participant, in order to reduce the possibility of selection bias.
Blinding (performance bias and detection bias) Clinicians	High risk	The initial intention was for a double-blind study, but due to the physical properties (appearance) of the trial product and the placebo, two of the clinical researchers were not blinded.
Blinding (performance bias and detection bias) Participants	Low risk	Stated that the participants were blinded to the preparations.
Blinding (performance bias and detection bias) Outcome assessors	Low risk	Those who carried out the laboratory analyses were blinded to both the participants and the preparations.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial did not state whether an intention-to-treat approach was used.
Selective reporting (reporting bias)	Unclear risk	The study outcomes were pre stated and the means to measure this as well. However, the means for validation of the measures to assess some of these outcomes were not stated.
Other bias	High risk	There is a concern with the block randomisation selection process as the clinical researchers were not sufficiently blinded to the physical properties of the intervention. This may have compromised the data collection process if the clinical researchers were the clinicians who observed the participants over the study period. There was no indication in the trial report that the clinical researchers were not the clinicians observing the participants.

Wambebe 2001

Methods	Randomised, placebo-controlled cross-over trial. Single-centre in Nigeria.
Participants	HbSS: 82 individuals. Age groups < 9 years, 10 - 19 years, 20 - 29 years, 30 - 39 years. > 3 painful or vaso-occlusive events in the preceding year.
Interventions	12 mg/kg/day Niprisan [®] versus placebo for 6 months (then cross-over for 6 months).
Outcomes	Mean hospital admissions, mean times health below average, mean times experienced mild to moderate pain, mean times experienced severe pain, mean times off work or school, haemoglobin, LFTs, Creatinine, BUN.
Notes	Funding source for the trial was not stated, although it was stated that NIPRID formulated the medications. Declarations of interest of the investigators also not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors report that participants were randomised into two treatment groups by 'simple random sampling'.
Allocation concealment (selection bias)	Low risk	The random sequence was concealed from participants and clinicians by a third party not directly involved with the trial.
Blinding (performance bias and detection bias) Clinicians	Low risk	Achieved by using an identical capsule as placebo, which was of the same colour and smell as the active formulation and was appropriate.
Blinding (performance bias and detection bias) Participants	Low risk	Achieved by using an identical capsule as placebo, which was of the same colour and smell as the active formulation and was appropriate.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and dropouts were reported in the trial and the numbers for each group given. The reasons given for dropouts were mainly due to incompleteness of health diary cards, although one participant was lost to follow-up. No information on the demographic composition of those who withdrew or dropped out was given and how this compared with the rest of the trial group. The trial did not state whether an intention-to-treat approach was used.
Selective reporting (reporting bias)	Unclear risk	The study outcomes were not explicitly pre-specified although the measures to obtain the reported outcomes were described in detail.
Other bias	Unclear risk	A washout period was not carried out as part of the design of the cross-over trial, and this has limited the interpretation of the results of the second six months of the trial. Further information is required to adequately address this issue. Most of the study participants were adolescents, although the age range was 2 - 42 years. This could affect the reporting of the primary outcomes such as the frequency of severe painful crises that are influenced by age.

BUN: blood urea nitrogen

HbSS: sickle cell anaemia

LFTs: lung function tests

Niprisan®: a freeze-dried extract of Piper guineenses seeds, *Pterocarpus osun* stem, *Eugenia caryophyllum* fruit and *Sorghum bicolor* leaves

PCV: packed cell volume

SS: homozygous sickle cell disease

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Doss 2016	Non-randomised with no control group Intervention: broccoli sprout homogenate Adults with diagnosis of hemoglobin HbSS or HbSβ° thalassemia by electrophoresis, were enrolled for this study at the Duke Comprehensive Sickle Cell Clinic and treated with different doses of broccoli sprout homogenate Outcome measures: tolerability, toxicity, and physiological effects of NRF2 activation
Kaddam 2015	Non-randomised with no control group Intervention: Gum arabic Participants with sickle cell anaemia were recruited from the out patients clinic of paediatric and adult haematology units in Military hospital-Khartoum-Sudan and treated with Gum arabic only Outcome measure: Hb F level
Panigrahi 1997	Non-randomised with no control group. Intervention: Yogaraj and Laxadi guguly and folic acid versus folic acid alone for 3 months. Post-Graduate Department of Shalya, National Institute of Ayurveda, Jaipur, Rajasthan Outcome measure: haemoglobin (g/dL)

Hb F: foetal haemoglobin

DATA AND ANALYSES

Comparison 1. Niprisan versus placebo or conventional treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events (at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Alanine amino-transferase (ALT) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Asparate amino-transferase (AST) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Alkaline phosphatase (ALP) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Gamma glutamine transferase (GGT) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Creatinine (umol/L)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Blood urea nitrogen (BUN) (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Level of haemoglobin (g/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Niprisan versus placebo or conventional treatment, Outcome 1 Adverse events (at 6 months).

Study or subgroup	NIPRISAN		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.1.1 Alanine amino-transferase (ALT) (IU)						
Wambebe 2001	27	12 (10.9)	25	13 (6)		-1[-5.74,3.74]
1.1.2 Asparate amino-transferase (AST) (IU)						
Wambebe 2001	27	40 (33.3)	25	33 (11)		7[-6.28,20.28]
1.1.3 Alkaline phosphatase (ALP) (IU)						
Wambebe 2001	27	84 (16.1)	25	82 (13)		2[-5.93,9.93]
1.1.4 Gamma glutamine transferase (GGT) (IU)						
Wambebe 2001	27	16 (10.9)	25	19 (9)		-3[-8.42,2.42]
1.1.5 Creatinine (umol/L)						
Wambebe 2001	27	78 (23.9)	25	77 (20)		1[-10.95,12.95]
1.1.6 Blood urea nitrogen (BUN) (mmol/L)						
Wambebe 2001	27	2.5 (1)	25	2.2 (1)		0.3[-0.25,0.85]
					Favours NIPRISAN	Favours placebo

Analysis 1.2. Comparison 1 Niprisan versus placebo or conventional treatment, Outcome 2 Level of haemoglobin (g/dL).

Study or subgroup	NIPRISAN		Placebo		Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)		
1.2.1 At 6 months						
Wambebe 2001	27	8.9 (2.2)	25	8.6 (5)		0.3[-1.83,2.43]
					Favours placebo	Favours NIPRISAN

Comparison 2. Ciklavit® versus placebo or conventional treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events (at 6 months)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Peri-orbital swelling	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Vomitting	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Diarrhoea	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Tiredness	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Abdominal distension	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Itching of the eyes	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Level of anaemia (PCV)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Ciklavit® versus placebo or conventional treatment, Outcome 1 Adverse events (at 6 months).

Analysis 2.2. Comparison 2 Ciklavit® versus placebo or conventional treatment, Outcome 2 Level of anaemia (PCV).

APPENDICES

Appendix 1. Search methods – current electronic searches

ISRCTN Registry search strategy

Date of Search: 26 July 2017

	Search terms
Search 1	sickle cell
Search 2	haemoglobinopathy OR haemoglobinopathies OR hemoglobinopathy OR hemoglobinopathies
Search 3	anaemia OR anemia
Search 4	thalassemia OR thalassaemia
Search 5	thalasemia OR thalasaemia
Search 6	haemoglobin OR hemoglobin
Search 7	depranocytosis
Search 8	anisocytosis
Search 9	meniscocytosis
Search 10	phytomedicine
Search 11	herbal remedies
Search 12	herbal extracts

AMED search strategy

(Continued)

Date of Search: 24 August 2017

Database / Resource	Strategy
AMED (EBSCOHST, 1985 to present)	S1 TX sickle S2 TX sickle-cell S3 TX meniscocytic S4 TX drepanocytosis S5 TX (hemoglobin s or haemoglobin s) S6 TX (hemoglobin sc disease OR haemoglobin sc disease) S7 TX (sickling AND (blood OR plasma)) S8 TX (hemoglobin c disease or haemoglobin c disease) S9 TX (hemoglobin d disease or haemoglobin d disease) S10 TX (hemoglobin e disease or haemoglobin e disease) S11 TX (hemoglobinopath* or haemoglobinopath*) S12 TX lepore S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 S14 (DE "PHYTOTHERAPY") S15 TX Ciklavir or Niprisan or Nicosan S16 TX seed* or leaf or leaves or plant* or flower* or stem* or root* or fruit* or herb* or phytomedicine* or phytotherap* or nutraceutical* or natural or food* or extract* or organic S17 S14 OR S15 OR S16 S18 S13 AND S17

WHO ICTRP search strategy
Date of Search: 27 July 2017

	Search terms
Search 1	sickle cell
Search 2	haemoglobinopathy OR haemoglobinopathies OR hemoglobinopathy OR hemoglobinopathies
Search 3	anaemia OR anemia
Search 4	haemoglobin AND sickle
Search 5	hemoglobin AND sickle

(Continued)

Search 6	thalassemia OR thalassaemia
Search 7	thalassemia OR thalassaemia
Search 8	depranocytosis
Search 9	anisocytosis
Search 10	meniscocytosis
Search 11	phytomedicine
Search 12	herbal remedies
Search 13	herbal extracts

ClinicalTrials.gov search strategy

Date of Search: 02 August 2017

	Search terms
Search 1	sickle cell
Search 2	haemoglobinopathy OR haemoglobinopathies OR hemoglobinopathy OR hemoglobinopathies
Search 3	anaemia OR anemia
Search 4	haemoglobin AND sickle
Search 5	hemoglobin AND sickle
Search 6	thalassemia OR thalassaemia
Search 7	thalassemia OR thalassaemia
Search 8	depranocytosis
Search 9	anisocytosis
Search 10	meniscocytosis
Search 11	phytomedicine
Search 12	herbal remedies
Search 13	herbal extracts

Appendix 2. Search methods – electronic searches for previous versions of this review

ISRCTN search strategy
Date of search: 17 January 2015

	Search terms
Search 1	sickle cell
Search 2	haemoglobinopathies OR haemoglobinopathy OR hemoglobinopathy OR hemoglobinopathies
Search 3	anaemia OR anemia
Search 4	thalassemia OR thalassaemia
Search 5	haemoglobin OR hemoglobin
Search 6	depranocytosis
Search 7	anisocytosis
Search 8	meniscocytosis
Search 9	phytomedicine
Search 10	herbal remedies
Search 11	herbal extracts

AMED search strategy
1985 to January 2015

1 exp HEMOGLOBINOPATHIES/
2 exp Hemoglobin, Sickle/
3 (hemoglobinopath\$ or haemoglobinopath\$).tw.
4 (thalassemia or thalassaemia).tw.
5 (hemoglobin h disease or haemoglobin h disease).tw.

6 lepre.tw.
7 lepre \$.au.
8 6 not 7
9 (barts and (blood or plasma)).tw.
10 hydrops fetalis.tw.

11 sickle cell.tw.
12 sickle-cell.tw.
13 meniscocytic.tw.
14 drepanocytosis.tw.
15 (hemoglobin s or haemoglobin s).tw.

16 (hemoglobin sc disease or haemoglobin sc disease).tw.
17 (sickling and (blood or plasma)).tw.

(Continued)

18 (hemoglobin c disease or haemoglobin c disease).tw.

19 (hemoglobin d disease or haemoglobin d disease).tw.

20 (hemoglobin e disease or haemoglobin e disease).tw.

21 (or/1-5) or (or/8-20)

WHAT'S NEW

Date	Event	Description
9 January 2018	New citation required but conclusions have not changed	Changes have been made throughout several sections of the review to incorporate the changes made following the addition of summary of findings tables.
9 January 2018	New search has been performed	Two trials have been added to the 'Excluded studies' section of the review. The quality of the evidence is now assessed according to the GRADE criteria - summary of findings tables have been included in the review.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 3, 2004

Date	Event	Description
26 March 2015	New search has been performed	Searches of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register, the International Standard Randomised Controlled Trial Number Register (ISRCTN) and the Allied and Complimentary Medicine Database (AMED), did not identify any potentially eligible trials.
26 March 2015	New citation required but conclusions have not changed	We have undertaken new searches for trials and made minor changes to the text throughout the review.
24 March 2014	Amended	Contact details updated.
12 December 2012	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any trials potentially eligible for inclusion in the review.
12 October 2012	New citation required but conclusions have not changed	The review has been updated with minor changes made throughout.
8 September 2010	New citation required but conclusions have not changed	The previous lead author (Nuno Cordiero) has stepped down from the review team and a new author has joined (Damian Co-hall). Oluseyi Oniyangi (previously co-author) is the new lead author for the review.
8 September 2010	New search has been performed	A new trial was identified by the search of the Group's Haemoglobinopathies Trials Register and has been added to the Included studies section of the review (Akinsulie 2005). No further trials were identified by the searches of the International Standard Randomised Controlled Trials Number Registry.

Date	Event	Description
		<p>A new Plain Language Summary has been included to replace the Synopsis as per Cochrane Collaboration guidelines.</p> <p>A new outcome - 'change in frequency of hospital admissions due to severe complications of sickle cell disease' has been added to the review. This is because not all severe complications of sickle cell disease may have been admitted into hospitals for treatment.</p>
7 November 2008	Amended	Converted to a new review format.
1 February 2006	New search has been performed	<p>The search of the Group's Haemoglobinopathies Trials Register identified one new reference to an already included trial (Wambebe 2001). This reference contained no further data or information that could be added to the review.</p> <p>Some minor statistical issues raised by the Group's statistician have been addressed.</p>

CONTRIBUTIONS OF AUTHORS

Nuno Cordeiro (NC) conceived review and until January 2010 acted as guarantor.
NC and Oluseyi Oniyangi (OO) drafted and completed the protocol.
NC and OO independently evaluated studies found by the searches and completed the review.

As from January 2010, OO became lead author and guarantor of the review. Damian Cohall (DC) joined the review team.

DECLARATIONS OF INTEREST

Both authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the initial protocol and review, the Jadad scale was used to assess the methodological quality of the included study. In the 2010 update, the new Cochrane risk of bias tool has been used to examine the quality and related risks of bias of the included studies.

A new outcome - "change in frequency of hospital admissions due to severe complications of sickle cell disease" has been added to the review. This is because not all severe complications of SCD may have been admitted into hospitals for treatment.

In the 2017 update, the GRADE approach was used to assess the quality of the evidence.

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Anemia [chemically induced]; Anemia, Sickle Cell [blood] [*drug therapy]; Antisickling Agents [adverse effects] [*therapeutic use]; Clinical Trials, Phase II as Topic; Plant Extracts [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans