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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	9
OBJECTIVES	10
METHODS	10
Figure 1.	12
RESULTS	13
DISCUSSION	19
AUTHORS' CONCLUSIONS	22
ACKNOWLEDGEMENTS	22
REFERENCES	23
CHARACTERISTICS OF STUDIES	26
DATA AND ANALYSES	32
Analysis 1.1. Comparison 1: Niprisan® versus placebo or conventional treatment, Outcome 1: Adverse events (at 6 months) ...	33
Analysis 1.2. Comparison 1: Niprisan® versus placebo or conventional treatment, Outcome 2: Level of haemoglobin (g/dL)	33
Analysis 2.1. Comparison 2: Ciklavit® versus placebo or conventional treatment, Outcome 1: Adverse events (at 6 months)	34
Analysis 2.2. Comparison 2: Ciklavit® versus placebo or conventional treatment, Outcome 2: Level of anaemia (PCV)	35
APPENDICES	35
WHAT'S NEW	39
HISTORY	40
CONTRIBUTIONS OF AUTHORS	41
DECLARATIONS OF INTEREST	41
SOURCES OF SUPPORT	41
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	41
INDEX TERMS	42

[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 updated version of a previously published Cochrane Review.

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: 17 March 2020; ISRCTN: 19 April 2020; AMED: 18 May 2020; ClinicalTrials.gov: 24 April 2020; 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

Three trials (212 participants) of three phytomedicines: Niprisan[®] (also known as Nicosan[®]), Ciklaviv[®] and a powdered extract of *Pfaffia paniculata* were included. The Phase IIB (pivotal) trial suggests that Niprisan[®] may be effective in reducing episodes of severe painful sickle cell disease crisis over a six-month period (low-quality evidence). It did not appear to affect the risk of severe complications or the level of anaemia (low-quality evidence).

The single trial of *Cajanus cajan* (Ciklavit®) reported a possible benefit to individuals with painful crises, and a possible adverse effect (non-significant) on the level of anaemia (low-quality evidence).

We are uncertain of the effect of *Pfaffia paniculata* on the laboratory parameters and symptoms of SCD (very low-quality of evidence).

No adverse effects were reported with Niprisan® and *Pfaffia paniculata* (low- to very 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 managing people with SCD and the results of its multicentre trials are awaited. Currently, no conclusions can be made regarding the efficacy of Ciklavit® and the powdered root extract of *Pfaffia paniculata* in managing SCD. Based on the published results for Niprisan® and in view of the limitations in data collection and analysis of the three trials, phytomedicines may have a potential beneficial effect in reducing painful crises in SCD. This needs to be further validated in future trials. More trials with improved study design and data collection are required on the safety and efficacy of phytomedicines used in managing SCD.

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. This is an update of a previously published Cochrane Review.

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: 18 May 2020 .

Study characteristics

Three trials (212 participants) and three phytomedicines Niprisan® (also known as Nicosan®), Ciklavit® and the powdered root extract of *Pfaffia paniculata* were included.

Key results

This review found that Niprisan® may help to reduce episodes of sickle cell disease crises associated with severe pain.

Ciklavit® may have little or no effect in reducing painful crises in SCD, and a possible adverse effect on the level of anaemia.

We are uncertain of the effect of the powdered root extract of *Pfaffia Paniculata* in SCD.

The three phytomedicine formulations reported no serious adverse symptoms or derangement of liver or kidney function in the participants. More scientifically robust 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 1. Summary of findings - Niprisan® versus placebo for SCD

Niprisan® compared with placebo for SCD

Patient or population: adults and children with SCD

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) ^a	⊕⊕⊕⊕ low^{b,c}	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) ^a	⊕⊕⊕⊕ low^{b,c}	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) ^a	⊕⊕⊕⊕ low^{b,c}	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 liver and renal function or in terms of serum creatinine levels.		NA	up to 80 (1 cross-over study) ^a	⊕⊕⊕⊕ low^{b,c}	Specific adverse events were not reported by treatment period so are not en-

Follow-up: 6 months					tered 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) ^a	⊕⊕⊕⊕ low^{b,c}
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) ^a	⊕⊕⊕⊕ very low^{b,c,d}
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).

Abbreviations: **CI**: confidence interval; **ITT**: intention-to-treat; **NA**: not applicable; **SCD**: sickle cell disease; **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.

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

Ciklavit® compared with placebo for SCD

Patient or population: adults and children with SCD

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^{a,b}	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^{a,b}	
Frequency of blood transfusion Follow-up: NA	Outcome not reported.			NA	NA	
Level of anaemia: packed cell volume Follow-up: 6 months	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	NA	87 (1 study)	⊕⊕⊕⊕ low^{a,b}	There was also no significant difference between treatment groups at

	difference was not statistically significant.		3 months, MD -1.52% (95% CI -3.49 to 0.45).
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).

Abbreviations: **CI:** confidence interval; **ITT:** intention-to-treat; **MD:** mean difference; **NA:** not applicable; **SCD:** sickle cell disease; **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.

a. Downgraded once due to risk of bias: concerns regarding lack of blinding of clinicians and unclear details regarding whether an ITT analysis was used and if outcome measures were validated.

b. Downgraded once due to applicability: study includes only children with HbSS genotype, not applicable to adults or individuals with other genotypes.

Summary of findings 3. Summary of findings - *Pfaffia paniculata* versus placebo for SCD

Pfaffia paniculata compared with placebo for SCD

Patient or population: children with SCD

Settings: out-patient

Intervention: 2 capsules of powdered roots of *Pfaffia paniculata*

Comparison: 2 capsules of corn starch as 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				
	Placeba	<i>Pfaffia paniculata</i>				
Frequency, severity or duration of painful crises	Less pain crises reported in the intervention group post treatment and compared to controls. No discrete data reported for either group.		NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered. Definition of clinical events not provided.
Follow-up: months 2, 3						

					Method of assessment of pain not provided.
Frequency of severe complications of SCD Follow-up: months 2, 3	The frequency of severe complications of SCD was less in the intervention group both post-treatment and compared to the control group.	NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered. Definition of clinical events not provided.
Frequency of hospital admissions from severe complications of SCD	Outcome was not measured.		NA	NA	
Any adverse events including hepatic and renal toxicity Follow-up: months 2,3	No adverse effects were reported in the intervention group.	NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered. Method of assessment of adverse events not provided.
Frequency of blood transfusion Follow-up: months 2,3	No need for blood transfusions in the intervention arm compared to the pre-treatment period of the same group and also to the control group post treatment.	NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered.
Level of anaemia: packed cell volume Follow-up: months 2,3	Increased levels of haematocrit and haemoglobin concentrations by 28% and 26% respectively were reported in the intervention arm. No changes in these parameters were observed in the control arm.	NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered.
Quality of life measures Follow-up: months 2,3	The intervention arm was reported to have improved mental and physical activities.	NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered. Method of assessment of quality of life measures not provided.
Number of sickle cells, peripheral erythroblasts and reticulocytes Follow-up: months 2,3	Reduction in the sickle cells, peripheral erythroblasts and reticulocytes of 60%, 63% and 50%, respectively, in the intervention arm at the end of the study period compared to baseline. No changes were observed in the placebo group.	NA	30 (1 study)	⊕⊕⊕⊕ Very low a,b,c,d	No discrete/continuous data entered.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Abbreviations: **CI:** confidence interval; **RR:** risk ratio; **SCD:** sickle cell disease.

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.

- a. Downgraded once due to risk of bias: poor data quality, attrition, lack of specificity on trial outcomes, the use of subjective assessments of clinical outcomes and lack of clarity on adherence to therapy.
- b. Downgraded once due to applicability: trial includes only children, not applicable to adults or reflective of general population of persons with SCD.
- c. Downgraded once due to applicability: the trial clinical outcome data inclusive of quality of life were not specified as outcome variables. Their measurements were neither recorded systematically nor were statistically robust.
- d. Downgraded once due to indirectness of evidence: Type of SCD was not specified, so not known which type of SCD trial results refer to.

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. Due to migration, persons affected with SCD are now found globally. It is estimated that 1 in 50 people in sub-Saharan Africa suffers from SCD (Davies 1997; Hickman 1999). The greatest burden of disease globally was found in three countries: Nigeria; Democratic Republic of Congo (DRC); and India (WHO 2010). It was estimated that 312,302 babies were delivered with SCD in 2010 (Piel 2013). This number is expected to increase to 400,000 annually by 2050 (Piel 2013). 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).

SCD has varying clinical manifestations and is associated with complications and a reduced life expectancy (Platt 1994). 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. 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 (β^+ or β^0) (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). SCD 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 (WHO 2010).

At present, there is no cure for SCD, although there are available modalities aimed at ameliorating its course. Available treatments such as bone marrow transplantation or gene therapy are out of reach of people most affected by the disease (WHO 2010). Apart from advice to avoid cold and dehydration, particularly during intercurrent illness, malaria prophylaxis in malaria endemic areas, good rest and nutrition, folic acid supplementation and the use of prophylactic antibiotics, and vaccination in children to prevent pneumococcal infection (Fleming 1989; Oniyangi 2006; Rankine-Mullings 2017; WHO 2010), there is little treatment on offer until an individual is symptomatic. Treatment is supportive, with analgesia and blood transfusion. This comprehensive healthcare package (CHCP) for SCD has been associated with significant reductions of morbidity and mortality, even in sub-Saharan Africa (Rahimy 2003; WHO 2010). 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 its 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).

Traditional medicines (including phytomedicines) which are easily available and accessible, as well as being culturally accepted are often used by up to 80% of families affected by SCD in low- and middle-income countries, especially for painful episodes and other SCD complications (Busari 2017; WHO 2010). This is especially so in sub-Saharan Africa, India and other low- and middle-income countries of the world, with the greatest burden of disease, but limited healthcare services (WHO 2010). Research has shown numerous potentially therapeutic agents with benefits for people with SCD (Amujoyegbe 2015; Imaga 2013; Vaishnava 2016). However, their use in SCD in these resource limited areas is not usually recommended by orthodox medical healthcare practitioners due to inadequate scientific knowledge of it (WHO 2010).

There is significant mortality from SCD (Lanzkron 2013; Makani 2011). 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 low- and middle-income 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 affected by SCD also have a reduced quality of life (McClish 2005).

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 SCD (Imaga 2013; Vaishnava 2016) and other ailments (Okigbo 2006; Verzar 1987), but there has been little

in the way of systematic appraisal of their benefits in randomised controlled trials (RCTs).

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). Ciklaviv® (*Cajanus cajan* seed extract as base) and *Zanthoxylum (Fagara) zanthyloides* have also been researched (Imaga 2013). *Pfaffia paniculata* was administered as a powdered extract of its roots in capsules (500 mg) (Araujo 2009). The antisickling properties of the plant's roots were investigated in vitro and validated (Ballas 2000; Mozar 2016). 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 blood cells from people with SCD have shown potentially clinically beneficial action of extracts of plants (Imaga 2013; Vaishnava 2016), 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, broccoli sprout homogenate and an extract of labdane diterpene from *Curcuma comosa* have been shown to increase Hb F production in red blood cells (Chokchaisiri 2010; Doss 2016; Kaddam 2015). The extract of the powdered root of *Pfaffia paniculata* is a sodium ionophore which has shown improvement of deformability and hydration of red blood cells (Araujo 2009; Mozar 2016). It was also reported to increase foetal haemoglobin (Hb F) (Araujo 2009). The methanolic extract of *Raphiostylis beninensis* stems has shown inhibition of haemolysis of red blood cells and an aqueous extract of *Lonchocarpus cyanescens* roots has shown moderate inhibition of haemolysis and improved deformability of red blood cells (Vaishnava 2016). The aqueous extract of *Monodora myristica* has been reported to increase the oxygen affinity of Hb S, and the leaves and unripe fruit of *Carica papaya* have shown slow inhibitory action on the haemolysis of red blood cells, while the seeds of *Wrightia tinctoria* have shown potent antisickling activity but the mechanism of action remains unknown (Vaishnava 2016).

Why it is important to do this review

Phytomedicines could be important for managing SCD, particularly in lower- and middle-income countries, 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. RCTs remain the gold standard in this regard.

This is an update of a previously published Cochrane Review (Cordeiro 2004; Oniyangi 2010; Oniyangi 2013; Oniyangi 2015; Oniyangi 2018).

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.

Further searching of trial registries: ISRCTN: 19 April 2020; ClinicalTrials.gov: 24 April 2020; and the WHO ICTRP: 27 July 2017

(attempted again in 23 April 2020 and 20 May 2020, but the registry was unavailable due to the COVID-19 pandemic).

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 phytotherapy).

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: 17 March 2020.

We also searched the following databases and trial registries:

- AMED EBSCOHost (Allied and Complementary Medicine; 1985 to 18 May 2020);
- ISRCTN Registry (www.isrctn.com; searched 19 April 2020);
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 24 April 2020);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 27 July 2017 (attempted again in 23 April 2020 and 20 May 2020, but unable to access the trial registry during the time of the review update due to the COVID-19 pandemic).

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 trials 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 phytotherapies 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.

Three 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](#); [Araujo 2009](#); [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 (ITT) 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 trial?
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 trial free of suggestion of selective outcome reporting?
6. Other potential sources of bias - was the trial 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 trial 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): All outcomes	Selective reporting (reporting bias)	Other bias
Akinsulie 2005	+	+	-	+	+	?	?	-
Araujo 2009	?	?	?	?	?	-	-	-
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 trials. All similar trials will be pooled using an OR and 95% CIs.

We will also perform an ITT 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 the Niprisan® and Ciklavit® trials in December 2009 and more recently, the authors of the *Pfaffia paniculata* trial in June 2020. Individual patient data among other discrete and continuous data on outcome variables were requested which we hoped to include in 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 three 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 three summary of findings tables; one for each comparison (Summary of findings 1; Summary of findings 2; Summary of findings 3).

All seven outcomes (see Types of outcome measures) are presented at the latest time point recorded (i.e. three months or 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 trial, indirectness of the evidence or imprecision of results (or both). We downgraded evidence by one level if we 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 seven trials, of which three (including a total of 212 participants) were eligible for inclusion (Akinsulie 2005; Araujo 2009; Wambebe 2001), three were excluded (Doss 2016; Kaddam 2015; Panigrahi 1997) and one is still ongoing (Abrams 2013).

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 trial 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 Sickle Cell clinic at Lagos University Teaching Hospital. This trial included children with 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.

Pfaffia paniculata extract versus placebo or conventional treatment

Trial design

This trial was a double-blinded randomised controlled trial comparing the safety and efficacy of a phytomedicine derived from the roots of *Pfaffia paniculata* (Brazilian ginseng), a perennial wild plant of the Amaranthaceae family, to placebo on children with SCD in an outpatient setting in Brazil (Araujo 2009). It was not stated in the paper how SCD was diagnosed. Neither the methods used for randomisation, nor details about the procedures for blinding were stated.

Informed consent was obtained from trial participants. However, it was not clear an assent process was used with the minors and adolescents. The trial protocol was approved by the Institutional Ethics Committee of the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Brazil, although no IRB number was provided.

Participants

The trial participants comprised 30 children with SCD. There were 15 children in each group - the intervention group had five males and 10 females with an average age of 14 years, while the control

group had six males and nine females with an average age of 15 years. It was not stated how SCD was diagnosed.

All trial participants had prior history of frequent abdominal, leg and skeletal pain and other sickle cell symptoms such as jaundice and leg ulcerations. There were no exclusion criteria stated.

Interventions

The participants of the intervention arm received two capsules orally, each containing 500 mg of the powdered root extract of *Pfaffia paniculata* at eight-hour intervals for three months; while the control arm received two capsules of placebo containing corn starch orally at the same dosing interval. There was no information on the concealment of intervention and how the dosage was determined.

Outcomes

The trial compared clinical outcomes and laboratory data of both the intervention and control arms for three months. The number of erythrocytes, reticulocytes, sickle cells, peripheral erythroblast, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and MCH concentration (MCHC) were measured immediately before, and two and three months after the start of treatment.

The authors reported on foetal haemoglobin, pain crises, other symptoms associated with SCD - priapism, lower limb ulcers, chest syndromes, skeletal and abdominal pain, frequency of blood transfusion, occurrence of pneumonia, adverse effects and quality of life indicators. There were no clear assessment and monitoring protocols established for these parameters.

The authors of the trial were contacted for more details regarding the trial, but no additional information was provided.

Excluded studies

Three trials were excluded (Doss 2016; Kaddam 2015; Panigrahi 1997). Although prospective, these trials were neither randomised nor controlled (or both); nor quasi-randomised or controlled (or both), as stated in the [Characteristics of excluded studies](#) table.

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 trial 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 trial 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 trial 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 ITT 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 trial objectives were listed as assessing the efficacy and safety of the intervention (Wambebe 2001). The trial 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 trial 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 trial 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 ITT 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 ITT analysis.

Selective outcome reporting

The trial 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 trial 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 trial 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 trial was compared to events occurring during the trial. 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.

Pfaffia paniculata versus placebo or conventional treatment

Allocation

Generation of allocation sequence

The trial was described as randomised, however, the method of randomisation was not stated (Araujo 2009). The trial authors were asked for more information about the randomisation process but no additional information was provided. We judge this as having an unclear risk of bias.

Concealment of allocation sequence

This was not described in the published trial report (Araujo 2009). The trial authors were asked for more information on the concealment of allocation sequence but they were unable to provide further details. We judge this as having an unclear risk of bias.

Blinding

This was described as double-blinded (Araujo 2009). However, there was no clarity if the capsules of the root extract were indistinguishable from the capsules of the placebo. The trial authors have been asked for more information on the adequacy of blinding process but they were unable to provide further details. We judge this as having an unclear risk of bias.

Incomplete outcome data

The authors have not provided discrete or continuous quantitative data on the trial outcomes. Furthermore, details of statistical analyses made were not provided in the trial report (Araujo 2009). Also, no consort diagram for the trial was included in the trial report. The trial authors have been asked for more information on outcome variables and the participants' adherence throughout the trial but they were unable to provide additional data. We judge this as having a 'high' risk of bias.

Selective outcome reporting

The outcome variables were stated to be both laboratory and clinical features of SCD in participants receiving the *Pfaffia paniculata* extract compared to placebo. While most laboratory parameters studied were pre-specified, the clinical outcomes were not explicitly stated. Foetal haemoglobin levels, though reported, were not pre-specified as one of the laboratory outcomes of the trial (Araujo 2009). Furthermore, clinical outcomes such as the symptomology of SCD, quality of life measures and adverse effects of the intervention were not stated as outcome variables but were reported in the results. We judge the risk of bias for this criterion to be 'high'. The trial authors were asked to clarify the selective reporting but were unable to comment.

Other potential sources of bias

The trial authors have not stated any potential sources of bias. However, we note that self-assessments for data collection relating to pain and quality of life measures may introduce bias as these are subjective assessments, and it was not stated how these observations were made. It was also not stated if and how adherence to the therapy was ascertained. Additionally, there was no confirmation of SCD diagnosis and no standardised definitions for the clinical events in this trial were outlined. We judge the risk of bias from this as 'high' and further information from the trial would be needed to adequately assess the efficacy and safety of the

intervention. The trial authors were asked for additional details to address these concerns but they were not able to comment.

Effects of interventions

See: [Summary of findings 1 Summary of findings - Niprisan® versus placebo for SCD](#); [Summary of findings 2 Summary of findings - Ciklaviv® versus placebo for SCD](#); [Summary of findings 3 Summary of findings - *Pfaffia paniculata* versus placebo for SCD](#)

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 additional data have 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. CIs 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 opine that the authors took all precautions to conceal the allocation. Therefore, we also report on their preliminary data below.

Despite our assessment of the risk of bias of the Araujo trial, we have provided a narrative summary of results of the trial (Araujo 2009). Discrete or continuous quantitative data were not provided in the report of the trial, but rather inferences were made with very limited report on the data analysis. These limit the applicability of the Araujo trial results in the final analysis and GRADE assessments of this review (Araujo 2009).

The quality of the evidence has been graded for those outcomes included in the summary of findings tables. For the definitions of these gradings, please refer to the summary of findings tables (Summary of findings 1; Summary of findings 2; Summary of findings 3).

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

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 $\mu\text{mol/L}$ (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

The comparability of the two groups was assessed pre-trial using the health diary, completed by trial 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

They reported there were 207 episodes of painful crises (mean 4.4, SD 10.3) before the trial, and 191 episodes (mean 4.2, SD 4.2) during the trial among the intervention group; and 109 episodes (mean 2.6, SD 50) before the trial and 164 episodes (mean 3.9, SD 4.3) during the trial 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 treatment 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

PCV 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

This outcome was not reported (Akinsulie 2005).

Pfaffia paniculata versus placebo or conventional treatment

One trial (30 participants) was eligible for inclusion (Araujo 2009).

Primary outcomes

1. Frequency, severity or duration of painful crises

The trial authors stated that the intervention arm exhibited less pain post-treatment, and also less than the control arm. Specifically there were less episodes of vaso-occlusive crises and priapism (very low-quality evidence) (Araujo 2009).

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

The trial authors stated that the intervention arm exhibited less incidence of lower limb ulceration and chest syndromes post-treatment and less than the control arm post-treatment. There was also less incidence of jaundice and thromboembolism in the intervention arm of the trial (very low-quality evidence) (Araujo 2009).

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 (Araujo 2009).

Secondary outcomes

1. Any adverse events including hepatic and renal toxicity

The authors reported that there were no adverse effects in the participants who received the extract of the powdered roots of *Pfaffia paniculata* (very low-quality evidence) (Araujo 2009).

2. Frequency of blood transfusion

It was reported that there were no need for blood transfusions in the intervention arm post-treatment and in comparison to the control group. However, the number of transfusions in the control arm was not stated (very low-quality evidence) (Araujo 2009).

3. Level of anaemia

Increased levels of haematocrit and haemoglobin concentrations by 28% and 26% respectively were reported in the intervention arm; while no changes in these parameters were observed in the control arm during the observation period (very low-quality evidence) (Araujo 2009).

4. Quality of life measures

Participants of the intervention arm were reported to have improved mental and physical activities and therefore an improved quality of life as compared to the control arm of the trial (very low-quality evidence) (Araujo 2009).

DISCUSSION

The Niprisan® trial was the first RCT to report on the use of phytomedicines in SCD (Wambebe 2001). The active formulation, Niprisan®, derived from plants indigenous to Nigeria, was previously assessed in in vitro and in animal studies (Adzu 2001; Awodogan 1996; Gamaniel 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 Ciklaviv® 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 underpowered to detect any but the largest effects. Moreover, as multiple comparisons are made, results of borderline significance are to be interpreted cautiously.

The Araujo trial with the powdered root extract of *Pfaffia paniculata* was also small and no power calculations were stated in the published report (Araujo 2009). This study was limited by the lack and quality of discrete and continuous data on the outcome variables. Unfortunately, the risk of bias, the subjectivity of the findings and participant demographics limit the applicability of the trial authors' reports of the root's anti-sickling properties and other improvements of laboratory and clinical outcomes in managing SCD (Araujo 2009). The trial authors were not able to address these concerns when contacted.

The main effect reported in the first two included trials (Akinsulie 2005; Wambebe 2001) was a reduction in severe pain episodes in those receiving the active formulations - Niprisan® and Ciklaviv®. 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 Ciklaviv® 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 (Akinsulie 2005; Wambebe 2001) 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 the Akinsulie and Wambebe trials only looked at people with HbSS and not other forms of SCD (Akinsulie 2005; Wambebe 2001). It is hoped that future trials will address this issue.

Summary of main results

We identified three trials that compared the effectiveness of phytomedicines (Niprisan®, Ciklavit® and *Pfaffia paniculata* extract) with placebo in SCD.

Niprisan®

The Niprisan® trial was the first RCT 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 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 (Akinsulie 2005). 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.

Pfaffia paniculata

The main finding reported in the *Pfaffia paniculata* trial was an increase in haematocrit, haemoglobin, erythrocytes and foetal haemoglobin as well as a reduction in the number of sickle cells, peripheral erythroblasts and reticulocytes in the intervention arm at the end of the study period compared to baseline (Araujo 2009). There were no reported changes in the placebo group. Less pain crises and symptoms of SCD were also reported in the intervention arm at the end of the treatment period compared to baseline. It was reported that the control participants in the placebo group continued to present several symptoms and complications related to SCD. No statistical comparisons were carried between the intervention and control groups

Other laboratory data indicated that MCV, MCH and MCHC did not change from baseline to end of the treatment period for all study participants.

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. The randomised controlled trials for Ciklavit® (Akinsulie 2005) and Niprisan® (Wambebe 2001) compared the efficacy of the phytomedicines to placebo in people with HbSS. There was no clarity in the *Pfaffia paniculata* trial about the participants' specific type of SCD diagnosis (Araujo 2009). 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 the three 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 sufficiently by the Ciklavit® (Akinsulie 2005) and Niprisan® (Wambebe 2001) trials to make an inference on the efficacy of the phytomedicines. 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 sufficiently in the three trials.

Both Ciklavit® and Niprisan® 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 *Pfaffia paniculata* trial was conducted in an outpatient setting in Brazil and no details on the use of other drugs by the participants were reported (Araujo 2009).

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. The participants of the other two trials were children/minors who were reported to have SCD. There was no confirmatory measure reported for sickle cell diagnosis for the participants in the *Pfaffia paniculata* trial. However, participants were not described as volunteers. They were randomised and blinded to the intervention which will limit any 'volunteer effects' as described above.

Furthermore, both the Ciklaviv® and Niprisan® trials had assessed only participants with HbSS, and as such the results of the review are not applicable to people with other sickle cell genotypes. The *Pfaffia paniculata* trial did not specify what form of SCD was diagnosed in the study participants. 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® and *Pfaffia paniculata* trials, although stated as randomisation. There was inadequate blinding of clinicians to the formulation used in the Ciklaviv® trial which was a potential source of bias. The *Pfaffia paniculata* trial was reported as being double-blinded but there was no clarification on the inability to distinguish the intervention treatment from placebo by the clinicians and participants. Furthermore, it was not stated in the three trials if an ITT 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 the Ciklaviv® and Niprisan® trials were people with HbSS, and therefore, the evidence generated from those trials may not be applicable to people with other forms of SCD. As the type of SCD affecting the participants of the *Pfaffia paniculata* trial was not stated, it was not possible to determine which SCD patient was intended to benefit from the trial's results.

Potential biases in the review process

The review included three trials assessing the usefulness of phytomedicines for managing SCD (Akinsulie 2005; Araujo 2009; Wambebe 2001). Other trials 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) of our review. Three studies were excluded from the review which assessed other phytomedicines for managing HbSS 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 very low- to low-quality evidence primarily due to poor generalizability to persons with sickle cell genotypes, unclear randomisation methods, lack of blinding, self-reported data and the lack of clarity on if an ITT 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® and *Pfaffia paniculata* trials reported within-group analysis, which is not as objective as an across-group analysis (Akinsulie 2005; Araujo 2009). We were unable to compare across intervention groups given the skewed nature of the Ciklaviv® trial data and the inadequate reporting of outcome variables in the *Pfaffia paniculata* trial; and from these, limited inferences were made regarding the trials.

Agreements and disagreements with other studies or reviews

There is a devoid of RCT studies with phytomedicines to treat SCD which are appropriately designed and powered for data analysis. However, some studies with limitations exist. There was one study on treatment of sickle cell disorders by ayurvedic medicine (Panigrahi 1997). Two additional studies were mentioned in the last review (Doss 2016; Kaddam 2015) about the use of broccoli sprout homogenate (Doss 2016) and Gum arabic (Kaddam 2015) as phytomedicines. We are awaiting the results of the RCT evaluating the use of vapourised cannabis for chronic pain associated with SCD (Abrams 2013).

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. *Pfaffia paniculata* is reported to have this effect as well (Araujo 2009). The mechanism

of 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 studies in the present review due to being neither randomised nor controlled trials; nor generated quality data to make appropriate inferences. They can therefore not be compared to the trials included in this Cochrane Review.

AUTHORS' CONCLUSIONS

Implications for practice

Niprisan®, Ciklaviv® and the powdered root extract of *Pfaffia paniculata*, phytomedicines for sickle cell disease (SCD), have been the subject of analysis in randomised controlled trials (Akinsulie 2005; Araujo 2009; Wambebe 2001). However, the 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. The *Pfaffia paniculata* trial was limited due to inadequate outcome data which limited any data analysis or suitable inferences.

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 for managing 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 Ciklaviv® or *Pfaffia paniculata*.

Based on the published results for Niprisan® and in view of the limitations in data collection and analysis of the trial, phytomedicines may have a potential beneficial effect in reducing painful crises in SCD. However, this needs to be further validated in future studies; more trials are required assessing the safety and efficacy of phytomedicines in managing SCD.

Therefore, at this stage, no recommendations can be made regarding the use 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 these phytomedicines in SCD, particularly with the lack of benefit noted in the across-groups analysis of Ciklaviv®. The poor quality of the outcome data in the *Pfaffia paniculata* trial must be averted in further studies.

The potential for an adverse effect of Ciklaviv® on anaemia needs to be clarified. There should also be clarity if the trials were powered sufficiently to detect adverse effects. 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akinsulie 2005

Study characteristics

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 Ciklaviv [®] or placebo. > 5 years: 20 mL twice-daily of Ciklaviv [®] 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	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. 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

Akinsulie 2005 (Continued)

		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.
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 ITT 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.

Araujo 2009
Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial. Out-patient setting in Brazil.
Participants	30 participants, of which 15 received the intervention and 15 received placebo. Intervention arm had 5 males and 10 females (average age of 14); placebo arm had 6 males and 9 females (average age of 15). All reported to have SCD. Method of confirmatory diagnosis not reported.
Interventions	Intervention arm received two capsules of powdered <i>Pfaffia paniculata</i> (500 mg/capsule) every 8 hours for 3 months. Placebo arm received two capsules of corn starch every 8 hours for 3 months.
Outcomes	Laboratory data: number of erythrocytes, reticulocytes, sickle cells, peripheral erythroblast, haemoglobin, haematocrit, MCV, MCH, MCHC and foetal haemoglobin Clinical data: incidence of pain crises, symptoms associated with SCD, frequency of blood transfusion, occurrence of pneumonia, adverse effects and quality of life indicators.

Araujo 2009 (Continued)

Notes The data collection and the analyses were not systematic. No discrete and continuous data were reported to provide a sufficient scientific inference from the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was randomised but the process was not disclosed. Trial authors were not able to provide additional information on request.
Allocation concealment (selection bias)	Unclear risk	Not described in the published report for the trial. Trial authors were not able to provide additional information on request.
Blinding (performance bias and detection bias) Clinicians	Unclear risk	The trial was described as double-blinded. However, there was no clarity if the capsules of the root extract were indistinguishable from the capsules of the placebo. Trial authors were not able to provide additional information on the adequacy of the blinding process on request.
Blinding (performance bias and detection bias) Participants	Unclear risk	The trial was described as double-blinded. However, there was no clarity if the capsules of the root extract were indistinguishable from the capsules of the placebo. Trial authors were not able to provide additional information on the adequacy of the blinding process on request.
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	The trial was described as double-blinded. The clinical outcome assessors are clinicians. However, there was no clarity if they were the investigators or concealed from the allocation sequence. Trial authors were not able to provide additional information on the adequacy of the blinding process on request.
Incomplete outcome data (attrition bias) All outcomes	High risk	The authors did not provide discrete or continuous quantitative data on the trial outcomes. There was no consort diagram for the trial or a report on attrition. Trial authors were not able to provide additional information on request.
Selective reporting (reporting bias)	High risk	The outcome variables were stated to be both laboratory and clinical features of SCD in participants receiving the <i>Pfaffia paniculata</i> extract, compared to placebo. Laboratory data was pre-specified in the report, however, clinical outcomes were not explicitly stated. Foetal haemoglobin levels was reported in the discussion of the trial report even though it was not reported in the results section.
Other bias	High risk	Self-assessments for data collection relating to pain and quality of life measures may introduce bias as this is a subjective assessment. Further, specific details were not provided about how these observations were made. There was no statement the adherence to the therapy. Additionally, there was no confirmation of sickle cell diagnosis and no standardised definitions for the clinical events for this study was outlined. Trial authors were not able to provide additional information on request.

Wambebe 2001

Study characteristics

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.

Wambebe 2001 (Continued)

> 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 ITT 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

ITT: intention-to-treat

LFTs: lung function tests

mean corpuscular haemoglobin: MCH

mean corpuscular haemoglobin concentration: MCHC

mean corpuscular volume: MCV

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

PCV: packed cell volume

SCD: sickle cell disease

SS: homozygous sickle cell disease

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Doss 2016	<p>Non-randomised with no control group</p> <p>Intervention: broccoli sprout homogenate</p> <p>Adults with diagnosis of haemoglobin 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</p> <p>Outcome measures: tolerability, toxicity, and physiological effects of NRF2 activation</p>
Kaddam 2015	<p>Non-randomised with no control group</p> <p>Intervention: Gum arabic</p> <p>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</p> <p>Outcome measure: Hb F level</p>
Panigrahi 1997	<p>Non-randomised with no control group.</p> <p>Intervention: Yogaraj and Laxadi guguly and folic acid versus folic acid alone for 3 months.</p> <p>Post-Graduate Department of Shalya, National Institute of Ayurveda, Jaipur, Rajasthan</p> <p>Outcome measure: haemoglobin (g/dL)</p>

Hb F: foetal haemoglobin

Characteristics of ongoing studies [ordered by study ID]

[Abrams 2013](#)

Study name	Vaporized Cannabis for Chronic Pain Associated With Sickle Cell Disease (Cannabis-SCD).
Methods	<p>Randomised quadruple blind placebo controlled cross-over trial.</p> <p>In-patient setting at the Clinical Research Center at SFGH, University of California, San Francisco, USA.</p> <p>Study phase: Phase I and II</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • SCD, including SS, SC, and Sb. • Ongoing opioid analgesic therapy for chronic sickle cell disease-associated pain. • Participants must be on a stable dose of analgesic medication (opioid or other) for at least 2 weeks before enrolment. • All men and women in this study must agree to use adequate birth control during this study. Acceptable barrier birth control methods are a male condom, female condom, diaphragm, or IUD. • All women of reproductive potential (who have not reached menopause or undergone hysterectomy, oophorectomy, or tubal ligation) must have a negative urine b-HCG pregnancy test performed before initiating the protocol-specified medication.

Abrams 2013 (Continued)

- Prior history of use of cannabis. Participants must have smoked cannabis on at least 6 occasions in their lifetime prior to enrolment.
- Participants will self-report abstaining from smoking or ingesting cannabis for one week prior to their enrolment into the study.
- Able to understand and follow the instructions of the investigator, including completing the pain intensity rating scales.
- Karnofsky Performance Scale > 60.
- Able and willing to provide informed consent.
- Able and willing to spend two separate periods of 5 days and 4 nights in the Clinical Research Center at SFGH.

Exclusion criteria:

- Severe coronary artery disease, uncontrolled hypertension, cardiac ventricular conduction abnormalities, orthostatic mean blood pressure drop greater than 24 mmHg, severe chronic obstructive pulmonary disease.
- Evidence of clinically significant hepatic or renal dysfunction based on judgment of physician.
- Positive serum THC level on Day 1 of study.
- Active substance abuse (e.g. alcohol or injection drugs) as determined by urine toxicity screening.
- Neurologic dysfunction or psychiatric disorder severe enough to interfere with assessment of pain or sensory systems.
- Current use of smoked tobacco products.
- Women who are pregnant or breast-feeding may not take part in this study.
- Unable to read or speak English.

Participants	34 people with SCD, including SS, SC, and Sb were included. The age of the participants were 18 years and older; and both sexes (males and females) were enrolled.
Interventions	<p>Drug: cannabis (other name: marijuana)</p> <ul style="list-style-type: none"> • Experimental arm: cannabis - vaporised cannabis with an approximately 1:1 ratio of THC: CBD. Contents of 1 cannabis cigarette (4.7% THC/5.1% CBD) was vaporised and inhaled. • Comparator arm: placebo - contents of 1 placebo cigarette (0% THC/0% CBD) was vaporised and inhaled. <p>Cannabis or placebo was taken for 5 days (12 p.m. on Day 1; 2 p.m. and 8 p.m. on Days 2 - 4; and 8 a.m. on Day 5), then cross over after 14 days for another 5 days of either placebo or cannabis, respectively.</p>
Outcomes	<p>Primary outcome: chronic pain levels</p> <p>Secondary outcomes:</p> <ol style="list-style-type: none"> 1. Short-term side effects associated with use of opioids for SCD; and 2. short-term effects on markers of inflammation and disease progression in people with SCD.
Starting date	August 2014 - May 19 2017.
Contact information	Donald I Abrams, MD, University of California, San Francisco, USA.
Notes	The trial is sponsored by the University of California, San Francisco, USA. The trial collaborators are NHLB and University of Minnesota, Minnesota, USA. The last update posted on the trial registry was on 2 May 2018. However, no trial report has been made public to date. Results for this study were returned to the investigators after the quality assurance review by ClinicalTrials.gov on 23 September 2019.

CBD: cannabidiol

IUD: intra-uterine device
 NHLB: National Heart, Lung, and Blood Institute
 Sb: sickle beta thalassaemia disease
 SC: sickle-hemoglobin C disease
 SCD: sickle cell disease
 Sβ: sickle beta thalassemia disease
 SFGH: San Francisco General Hospital
 SS: sickle cell anemia
 THC: delta-9-tetrahydrocannabinol

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
1.1 Adverse events (at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.1 Alanine amino-transferase (ALT) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.2 Asparate amino-transferase (AST) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.3 Alkaline phosphatase (ALP) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.4 Gamma glutamine transferase (GGT) (IU)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.5 Creatinine (umol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.6 Blood urea nitrogen (BUN) (mmol/L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Level of haemoglobin (g/dL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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

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

Comparison 2. Ciklavit® versus placebo or conventional treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Adverse events (at 6 months)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.1 Peri-orbital swelling	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.2 Vomitting	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.3 Diarrhoea	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.4 Tiredness	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.5 Abdominal distension	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.6 Itching of the eyes	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2 Level of anaemia (PCV)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2.1 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2.2 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

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 – electronic searches for the current version of this review

ISRCTN Registry search strategy

Date of Search: 19 April 2020

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	thalassemia OR thalassaemia
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

Phytomedicines (medicines derived from plants) for sickle cell disease (Review)

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(Continued)

Date of Search: 18 May 2020

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

ClinicalTrials.gov search strategy
Date of Search: 24 April 2020

	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

(Continued)

Search 7	thalasemia 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 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 thalassaemia
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

WHAT'S NEW

Date	Event	Description
18 September 2020	New search has been performed	<p>We identified one potentially-eligible trial from a search of the Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register (17 March 2020). The trial was included after it was assessed and was determined to meet the review's inclusion criteria (Araujo 2009).</p> <p>We undertook a new search (18 May 2020) of the Allied and Complementary Medicine Database (AMED) database and identified 112 references, which were discarded as not relevant.</p> <p>We also undertook further searching of trials registries: ISRCTN: 19 April 2020; ClinicalTrials.gov: 24 April 2020; and the WHO IC-TRP: 27 July 2017 (attempted again on 23 April 2020, but unable to access the registry due to the COVID-19 pandemic).</p> <p>One trial was identified in the ClinicalTrials.gov registry investigating the use of vapourised cannabis for chronic pain associated with sickle cell disease. The last update posted on the trial registry was on 02 May 2018. However, no trial report has been made public to date. Results for this trial were returned to the investigators after a quality assurance review by ClinicalTrials.gov on 23 September 2019, we have included it in the Characteristics of ongoing studies.</p>
18 September 2020	New citation required but conclusions have not changed	We updated the searches, included on new trial and made minor changes to the text throughout several sections of the review.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 3, 2004

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.
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 Complementary 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.

Date	Event	Description
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 Cohall). Oluseyi Oniyangi (previously co-author) is the new lead author for the review.
8 September 2010	New search has been performed	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.
7 November 2008	Amended	Converted to a new review format.
1 February 2006	New search has been performed	Some minor statistical issues raised by the Group's statistician have been addressed.

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

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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 and 2020 updates, the GRADE approach was used to assess the quality of the evidence.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Infant; Male