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Review

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Safety and efficacy of herbal medicines for the management of sickle cell disease in Africa: a systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis evaluated the safety and efficacy of herbal remedies used to manage sickle cell disease (SCD) in Africa. Before the advent of western medicine, people depended on herbal medicines for treating different illnesses. Using herbal medicines to sickle cell disease (SCD) is still common in Africa. However, data on the safety and efficacy of any of these remedies are limited. We searched PubMed, Embase, Google Scholar and Web of Science from inception to 11th January 2024 using the keywords "herbal medicine" and "sickle cell" and the name of each of the countries in Africa without language restrictions. We included cross-sectional studies that reported the safety or efficacy of herbal medicine for managing sickle cell disease. Two reviewers assessed all included studies for suitability for inclusion in this review. All included articles were assessed using ROBINS-1, a tool for assessing the risk of bias in non-randomized studies of interventions. We used the random-effect model to pool the efficacy and safety profiles of the herbal medicines using RStudio version 4.2.2. Overall, we included five studies involving 1,489 individuals with SCD. Of these, 789 (53.0%) used herbal remedies like Aloe barbadensis (Aloe vera), Zingiber officinale (ginger), Cymbopogon citratus (lemongrass), Forever Living products, Golden Neo-Life Diamite International (GNLD) diet supplements and ginseng products. About 22.9% (181 out of 789) of the participants who used herbal remedies reported side effects, while 38.5% (304 out of 789) reported improving their symptoms. There was a high risk of publication bias in the articles included in this review. The pooled adverse effects of the herbal medicines for SCD treatment were 48% lower (Odds ratio: 0.52, 95% confidence interval (CI): 0.26 - 1.05, I^2= 82%, p<0.01) while the pooled efficacy of herbal remedies for treating SCD was nearly 100% higher (odds ratio= 2.07, 95% confidence interval 0.99 - 4.32, I^2= 78%, p<0.01) among the users than controls. However, these findings were not statistically significant. Our findings indicate no significant difference in the safety and efficacy of herbal medicines among people with SCD who used or did not use herbal remedies. However, the sample sizes of the primary studies were small. Thus, more extensive controlled studies with better-defined endpoints are required to inform the use of herbal medicines in managing SCD in Africa.

Introduction

Sickle cell disease (SCD) is a group of haematological disorders associated with the polymerisation of haemoglobin within red blood cells, leading to the sickling of red blood cells under low oxygen tension [1]. This polymerisation reduces the flexibility of the red blood cells, clogging tiny capillaries and further lowering oxygen tension in end organs. In addition, acute vaso-occlusive pain is caused by the entrapment of erythrocytes and leucocytes in the microcirculation, causing vascular obstruction and tissue ischaemia [1]. Traditional healing practices, including the usage of herbal medicines, have been embedded into the cultural fabric of the African people, offering alternative health care for different ailments [2,3]. It is also known that herbal remedies for SCD treatment are sold without regulation in some marketplaces [4-6] or distributed within communities in Africa [6-8]. However, the pooled prevalence of use of herbal medicines for the treatment of SCD in Africa is only 59% [9] and effectively reduces the frequency of SCD [4,10-13].

Examples of herbal drug used in the management of SCD include *Zanthoxylum Chalybeum, Carissa edulis, Ficus capensis, Niprisan, Cajanus cajan, Petiveria alliacaea, Chenopodium ambrosioides, Entandrophragma utile, Aloe barbadensis (Aloe vera), Zingiber officinale (ginger), Cymbopogon citratus* (lemongrass), forever living products, Golden Neo-Life Diamite International (GNLD) diet supplements and ginseng products among others [4,10-16]. Animal studies have indicated adverse events while using some of these herbal remedies. For example, *Zanthoxylum chalybeum* bark extract was tested in laboratory rats and shown to cause significantly higher total white blood cell counts, predominantly lymphocytes and associated neutropenia [17]. Although low-dose extract was safer, higher-dose extracts were associated with elevated creatinine levels and the histology picture showed Squamous cell growths in the large and small intestines in 100% of the tested animals [17]. High doses of *Carissa edulis* root and bark extracts were associated with drug-induced mild renal, hormonal, haematological and biochemical changes in laboratory rats [18].

Similarly, *Ficus capensis* leaf extracts have high erythropoietic and anti-sickling properties [19]. Niprisan was associated with headaches [15,16]. In some patients, *C. cajan* was linked to gastrointestinal symptoms [8]. At the same time, *Aloe barbadensis* (Aloe vera), *Zingiber officinale* (ginger), *Cymbopogon citratus* (lemongrass), forever living products, GNLD (Golden Neo-Life Diamite International) diet supplements and ginseng products caused fever and diarrhoea [12]. On the other hand, some herbal remedies, like *Petiveria alliacaea*, *Chenopodium ambrosioides* and *Entandrophragma utile*, had no side effects reported yet [10]. Hydroxyurea and folic acid are the most prescribed medicines in many African sickle cell clinics. Hydroxyurea, also known as hydroxycarbamide, is an oral chemotherapeutic agent used to manage cancer and sickle cell disease [20,21]. It activates the gamma gene to increase the production of fetal hemoglobin (HbF), thereby diluting the concentration of Hanks' Balanced Salt Solution (HBSS), resulting in the reduced frequency of sickle cell crisis [22-24]. It also enhances urine concentrating ability and lessens renal enlargement, suggesting some benefits to renal function [25]. In addition, it reduces the number and severity of painful crises and blood transfusions and increases foetal haemoglobin production [26]. However, hydroxyurea is associated with neutropenia, bone marrow suppression, hepatic enzyme elevation, anorexia, nausea, vomiting and reversible dose-dependent leucopenia [26,27]. Therefore, despite the benefits, the use of hydroxyurea requires close monitoring and dose adjustments accordingly.

Despite the wide availability and frequent use of herbal medicine in SCD management [5,8,28], data on the safety and efficacy of these remedies in Africa are limited. In addition, what happens when it is used over a prolonged period is also unknown. Therefore, this systematic review and meta-analysis were conducted to evaluate the safety and efficacy of the available herbal remedies used to manage sickle cell disease in Africa.

Methods

This review was conducted according to the guidelines for systematic reviews and Meta-analyses of Observational Studies in Epidemiology (MOOSE) [29].

Registration of the protocol

Our study protocol was registered with PROSPERO (number CRD42022346766) and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline for network meta-analyses [30].

Search strategy

This review generated a question using the Condition, Context, and Population (CoCoPop) guidelines by the Joanna Briggs Institute [31]. The condition was "safety and efficacy of herbal

medicines for the treatment of SCD," the context was "Africa" and the population was "individuals living with SCD". Therefore, the research question was: "what is the safety and efficacy of herbal medicines used to treat sickle cell disease in Africa?" The following keywords were used to identify potential articles on 11th January 2024 from *PubMed, Embase, Google Scholar* and *Web of Science*: "sickle cell", "herbal medicine" and "Africa". The search included papers from the date of database inception to 11th January 2024. The search strategy is presented in Figure 1.

Eligibility criteria

All identified articles were entered into Endnote for screening and removal of duplicates. The screen adhered to the criteria in Table 1 below. Two authors independently screened the title and abstract of each article and in case of any discrepancies, the third author made the final decision by consensus.

Data extraction

Two authors independently screened the full-text for risk of bias and extracted data. The data extracted from each article included details of the authors, year of publication, sample size, number of individuals using herbal medications to treat SCD, study design, study setting (Country and city), type of herbal medication used and the effects reported.

Quality appraisal

All articles were assessed using the ROBINS-1, a tool for assessing the risk of bias in non-randomized studies of interventions [32]. Seven bias domains were assessed and graded as low, moderate or serious depending on the gravity of the risk of bias. Seven risks of bias domains were identified and assessed online [33]. There was a serious overall risk of publication bias as shown in Figure 2.

Sample size calculation

There was no sample size calculation performed. All articles which met the inclusion criteria and were published during the study period were included. The number of articles included influenced the multivariable and logistic regression analysis. It was not possible to perform adequate sensitivity analysis with less than 10 articles included in the review study.

Data analysis

This was performed using RStudio version 4.2.2. Categorical data from each study were summarized as frequencies and percentages, and continuous data as mean and standard deviation. In addition, we calculated estimates of safety and efficacy as standardized mean difference (M.D.) and odds ratio (OR) with the corresponding 95% confidence intervals between studies. The heterogeneity across individual studies was tested using Higgins's inconsistency Q statistics. Finally, the random effect in the meta-analysis was performed for pooled outcomes and, as reported: I^2. The statistic is interpreted as negligible (I^2= 0%), minimal (I^2< 20%), moderate (20% < (I^2<50%) and substantial (I^2> 50%).

All the results were presented as forest plots and visual assessment of small-study effects, typically contour-enhanced funnel plots, were shown to detect the presence of publication bias of the authors. A systematic narrative synthesis was performed to complete the meta-analysis, and p< 0.05 was considered statistically significant. Risk of bias plots were generated. Given this systematic review's limited number of studies, sub-group sensitivity analysis was not performed.

Results

Search results

We identified 277 articles, screened and retrieved twenty-three articles. Five articles satisfied the inclusion criteria and were retained for the meta-

analysis. Two hundred and seventy-two were excluded. A summary of the data extraction processes is outlined in Figure 1.

Characteristics of studies excluded from this review

All the excluded studies were reviews [34-42], in vitro studies [19,43-45], observational trials [14-16] and animal studies [17,18] using the herbal medicines commonly used for sickle cell treatment. Details are in Table 2.

Characteristics of included studies

All the included studies were conducted in Nigeria (n= 3) [10-12] and Uganda (n= 2) [4,13]. The studies were cross-sectional, with each sample size of at most 415 participants (Table 3).

Herbal medicines used for the treatment of sickle cell disease

Seven hundred seventy-nine participants used herbal medicines, while 700 did not. The commonly studied herbal medicines were *Aloe barbadensis* (Aloe vera), *Zingiber officinale* (ginger), *Cymbopogon citratus* (lemon grass), and ginseng products, *P. alliacaea, C. ambrosioides, E. utile*, Forever Living products, Golden Neo-Life Diamite International (GNLD) diet supplements and other commonly marketed products on television and radio from the years 2008 to 2023.

Safety of herbal medicines used for the treatment of sickle cell disease

The reported safety concerns ranged between 5.6% [12] and 31.9% [13]. Other safety concerns included gastrointestinal symptoms such as diarrhoea, vomiting and abdominal distension (Table 1). Approximately 22.9% (181 out of 789) of the participants who used herbal remedies had adverse effects.

Pooled safety of herbal medicines used among persons with sickle cell disease

For the studies [4,10-13], the pooled adverse effects (safety concerns) of the herbal medicines for sickle cell disease treatment were 48% lower (odds ratio: 0.52, 95% confidence interval (CI): 0.26 - 1.05, I^2= 82%, p < 0.01) among participants who used them than controls. However, the difference was not statistically significant, as shown in Figure 3.

Publication bias for safety concerns for herbal remedies for the treatment of sickle cell disease

Four of the five studies are in the white region of the contour-enhanced funnel plots, showing high publication bias (Figure 4).

Because of the few articles in this review, it was impossible to perform an adequate sensitivity analysis of the few articles included.

Efficacy of herbal medicines used for the treatment of sickle cell disease

All studies [4,10-13] (Table 1) reported improvement in the general health of the people living with SCD and reduced frequency of sickle cell crises.

Pooled efficacy of herbal medicines among persons with sickle cell disease

Different studies used different herbal medicines and reported on various parameters. The pooled efficacy of herbal remedies for treating sickle cell disease was nearly 100% (odds ratio= 2.07, 95% confidence interval 0.99 - 4.32, I^2= 78%, p<0.01) higher among the users than controls, details in Figure 5. Again, this was not statistically significant.

Using the contour-enhanced meta-analysis funnel plot, three of the five studies show statistical significance (p < 0.01), suggesting that the funnel plot asymmetry could be due to publication bias, as shown in Figure 6.

However, because of the few articles in this review, performing an adequate sensitivity analysis of the few articles included was impossible.

Discussion

Findings in context

This systematic review and meta-analysis found that the common herbal remedies used for treating sickle cell disease were *Aloe barbadensis* (Aloe vera), *Zingiber officinale* (ginger), *Cymbopogon citratus* (lemongrass), ginseng products, *P. alliacaea, C. ambrosioides, E. utile*, Forever living products, GNLD diet supplements [4,10-13]. Furthermore, we found that fewer people with sickle cell disease who received herbal medicine treatment got some side effects from the herbs. Overall, we found no statistical difference in efficacy and safety concerns among people with sickle cell disease who received herbal medicines compared to those who did not.

Herbal medicine for the treatment of sickle cell disease is widely available and sold in some African markets [5,8,28]. However, our study found no statistical differences in safety and efficacy for their use. In a systematic review of the use of hydroxyurea in sub-Saharan Africa, one dose-limiting effect occurred per five patient-years of treatment [46]. That is much less than the prevalence of undesired effects compared to herbal therapy in this systematic review.

Niprisan, made from pepper, sorghum, clove flower buds and trona [47], has antisickling properties and has been shown to reduce the number of sickle cell crises in Nigeria [15,16]. Pigeon peas (Cajanus cajan) are a common foodstuff in sub-Saharan Africa and have also been shown to reduce the number of sickle cell crises in Nigeria [14]. In the USA, there is growing evidence that herbal medicines are efficacious, but data on safety is scanty [48].

They commonly used ginkgo, garlic, St. John's wort, soy and kava [48]. St. John's worth is extracted from the flowers of *Hypericum perforatum* and contains hyperforin and hypericin with anxiolytic, sedative, antidepressant and analgesic effects [49]. Ginger (Zingiber officinale) is used in most Asian countries for soothing muscle pain and swelling, arthritis, headaches and digestive and appetite problems [49]. So, these herbs may relieve pain symptoms of sickle cell crises.

In Asia, herbal medicine therapy is part of mainstream conventional medicine [49,50]. They used Jiawei niantong capsules (herbal medicine for treating pain). These capsules were found to have fewer side effects and were more efficacious compared to conventional drugs used for pain management [51]. The capsule contains a mixture of *Corydalis ternate, Cyperus rotundus, Panax notoginseng, Aquilaria malaccensis, Curcuma phaeocaulis, Citrus deliciosa, Nardostachys jatamansi, Dracaena cinnabari, Rheum palmatum* and *Dryobalanops aromatica* [51]. Therefore, this may explain the motivation for using herbal remedies in Africa.

Limitations and weakness of the study

Five studies were included in this systematic review and meta-analysis. Therefore, it was impossible to perform a sensitivity analysis. Only the English databases were searched. That could have excluded other bases like Chinese and Indian databases were herbal medicines are popular. The articles had high heterogeneity for safety at 82% and efficacy at 78%, respectively, for empirical studies on herbal medicines for managing SCD in Africa, but these were not statistically significant.

Conclusion

Our findings reveal no significant difference in the safety and efficacy of herbal medicines among people with sickle cell who used or did not use herbal remedies. However, our sample size was small and thus, more extensive future studies with

better-defined endpoints are required to inform the use of herbal medicines in managing sickle cell disease in Africa.

What is known about this topic

- *Before the advent of Western medicine, Africans used herbal medicines to treat all ailments, including sickle cell disease - herbal medicines still treat sickle cell disease in Africa;*
- *To date, herbal medicines for treating sickle cell disease are sold in some African markets.*

What this study adds

- *In this study, we found no significant difference in the safety and efficacy of herbal medicines among people with sickle cell who used or did not use herbal remedies;*
- *However, few studies have examined the safety and efficacy of herbal medicines among people with sickle cell disease in Africa.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Silvia Awor drafted the research protocol, registered it in Prospero, did data extraction and screening processes and drafted the manuscript. Ronald Kivumbi and Benard Abola participated in data screening, did the meta-analysis and reviewed the manuscript. Felix Bongomin provided expert advice on the subject, did data screening and analysis and reviewed the manuscript. Mark Mohan Kaggwa did data extraction and reviewed the manuscript. Francis Pebolo Pebalo proofread and reviewed the manuscript. David Musoke, Geoffrey Maxwell Malinga, Proscovia Nnamuyomba, Jackie Epila, Acaye Ongwech and Christine Oryema guided the protocol writing and reviewed the manuscript. All authors have read and agreed to the final manuscript.

Tables and figures

Table 1: eligibility criteria employed

Table 2: characteristics of studies excluded from this review

Table 3: safety and efficacy of herbal medicines for treating Sickle cell disease in Africa

Figure 1: flow diagram for data extraction (the PRISMA diagram)

Figure 2: risk of bias domain for the safety and efficacy of herbal medicine used for the treatment of sickle cell disease in Africa

Figure 3: forest plot of safety herbal remedies for sickle cell disease treatment in Africa

Figure 4: contour-enhanced funnel plot for the safety of the herbal remedies at 90% 95% and 99% confidence intervals for the treatment of sickle cell disease in Africa

Figure 5: forest plot of the efficacy of herbal remedies for the sickle cell disease treatment in Africa

Figure 6: contour-enhanced funnel plot of the efficacy of the herbal remedies at 90%, 95% and 99% confidence intervals for the treatment of sickle cell in Africa

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Table 1: eligibility criteria employed

Inclusion criteria	**Exclusion criteria**
Observational studies reporting the safety or efficacy of herbal medicine use in SCD treatment in Africa,	Peer-reviewed. Case reports, editorial, and qualitative studies were excluded
English language	Textbooks, non-peer-reviewed work
Peer-reviewed published literature	Non-human subjects / participants
Published from inception to 11th January 2024	
Full text available	
Studies identified as primary research	

Table 2: characteristics of studies excluded from this review	
Article	**Reason for exclusion**
N. O. A. Imaga 2010 [35]	Review article about plants with antisickling activity
Afolabi *et al.* 2016 [40]	Review article about the distribution of antisickling plants
Cordeiro NJ, Oniyangi O 2004 [34]	Review article about the niprisan trials in Nigeria, registered in the Cochrane database
Oniyangi O, Cohall DH 2010	Cochrane review of trials on niprisan and Cajanus cajan [14, 15]
Oniyangi O, Cohall DH 2013	Cochrane review of trials on niprisan and Cajanus cajan [14, 15]
Oniyangi O, Cohall DH 2015	Cochrane review of trials on niprisan and Cajanus cajan [14, 15]
Oniyangi O, Cohall DH 2018	Cochrane review of trials on niprisan and Cajanus cajan [14, 15]
Oniyangi O, Cohall DH 2020 [42]	Cochrane review of trials on niprisan and Cajanus cajan [14, 15]
Ameh *et al.* 2012 [37]	Review article on the traditional management of sickle cell disease in Nigeria
Adzu *et al.* 2015 [43]	In vitro study about the effect of niprisan
Folasade *et al.* 2006 [44]	Analysis to find the composition of Herbal extracts used for management of sickle cell disease
Mojisola *et al.* 2020 [45]	Testing the antisickling activity for the herbal extracts used for treating sickle cell disease in Nigeria
Umeokoli *et al.* 2013 [19]	Testing the antisickling activity for a herbal extract used for treating sickle cell disease in Nigeria
Akinsulie *et al.* 2005 [14]	Clinical trial of Cajanus cajan already reviewed in the Cochrane database [42]
Wambebe *et al.* 2001 [15]	Clinical trial for niprisan, already reviewed in the Cochrane database [34, 36, 38, 39, 41, 42]. All participants received the intervention at the end of the study. Thus made it difficult to define endpoints of the study variables to include in this review
Wambebe *et al.* 2001 [16]	All participants received the intervention at the end of the study. Thus made it difficult to define endpoints of the study variables to include in this review
Ogwang *et al.* 2008 [17]	Testing the toxicity of a herbal extract in rats
Ya'u *et al.* 2013 [18]	Testing the toxicity of a herbal extract in rats

Table 3: safety and efficacy of herbal medicines for treating sickle cell disease in Africa

Authors	Setting & design	Sample N(n)	Used herbs	Herbal remedy	Safety profile	Efficacy
Apolot et al., 2023 [15]	Cross-sectional study	372	155	aloe vera, ginger, lemongrass, Aframomum meleguet, garlic, Carica papaya, Sorghum bicolor, Cajanus cajan seeds, piper guineensis, pterocarpus osun, eugenia caryophyllala (cloves), and fagara (f. zanthoxyloide)	Reported side effects (n=40, 25.8%)	Reported more effective pain relief (n=68)
Lubega et al., 2021 [13]	Cross-sectional study	384	298	Herbal medications commonly marketed over radio and television	Reported side effects (n=95, 31.9%)	Reported more effective relief of pain (n=70)
Busari et al., 2017 [11]	Cross-sectional study	200	177	Forever Living, Zingiber officinale (ginger), GNLD, Cymbopogon citratus (lemongrass), ginseng, diet and supplements	Reported side effects (n=15, 8.5%)	Improved general health (n=144)
Amoran et al., 2017 [12]	Cross-sectional study	415	123	Herbal medications commonly marketed in their communities	Reported side effects (n=29, 23.6%)	Reduced the frequency of crises (n=12)
Oshikoya et al., 2008 [14]	Cross-sectional study	118	36	Aloe barbadensis (Aloe vera), Zingiber officinale (ginger), Cymbopogon citratus (lemongrass), and ginseng products	Fever, diarrhoea (n=2, 5.6%)	Improved general health (n=10)

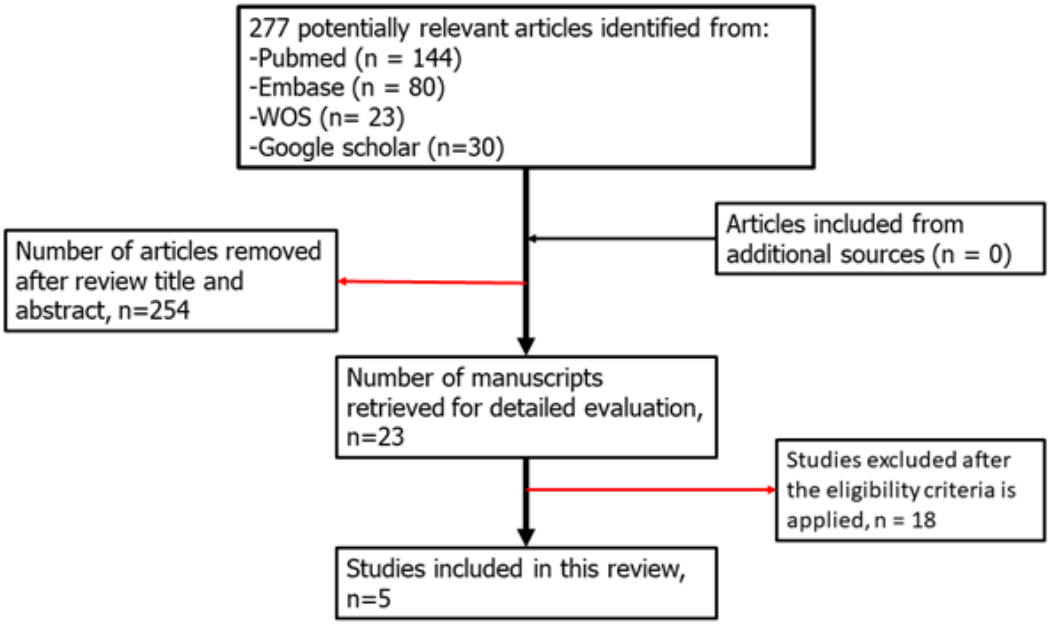

Figure 1: flow diagram for data extraction (the PRISMA diagram)

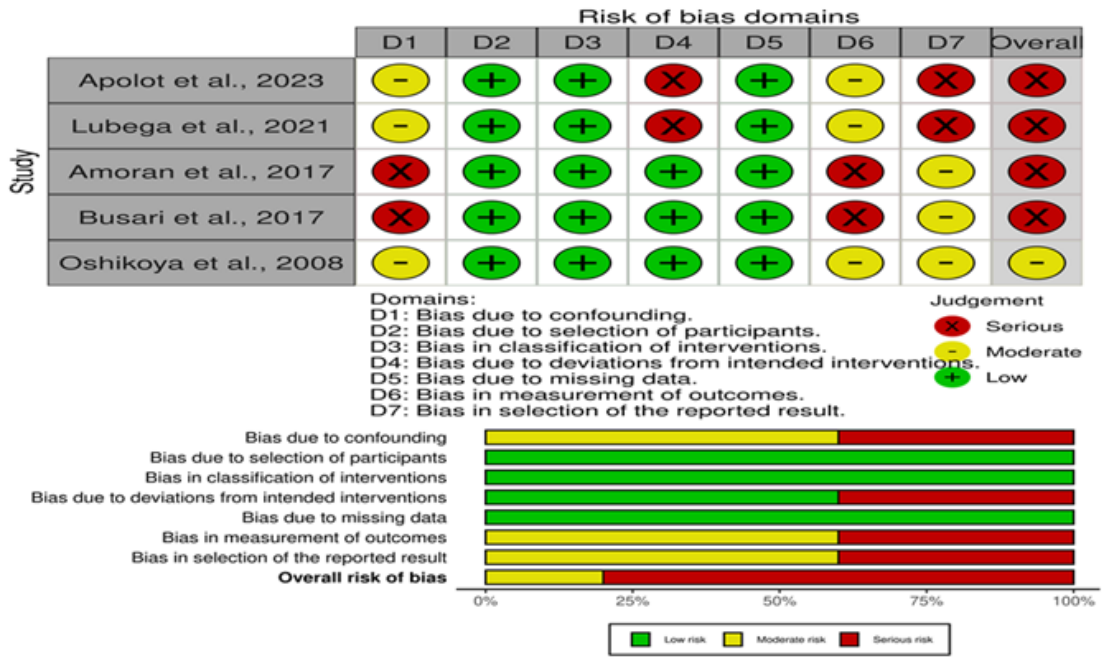

Figure 2: risk of bias domain for the safety and efficacy of herbal medicine used for the treatment of sickle cell disease in Africa

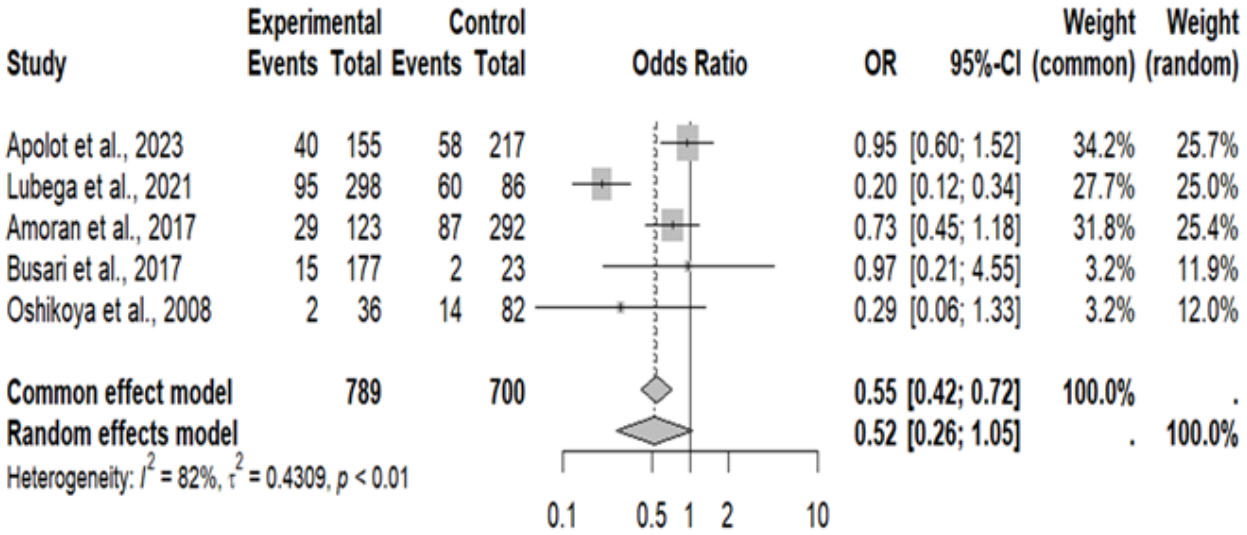

Figure 3: forest plot of safety herbal remedies for sickle cell disease treatment in Africa

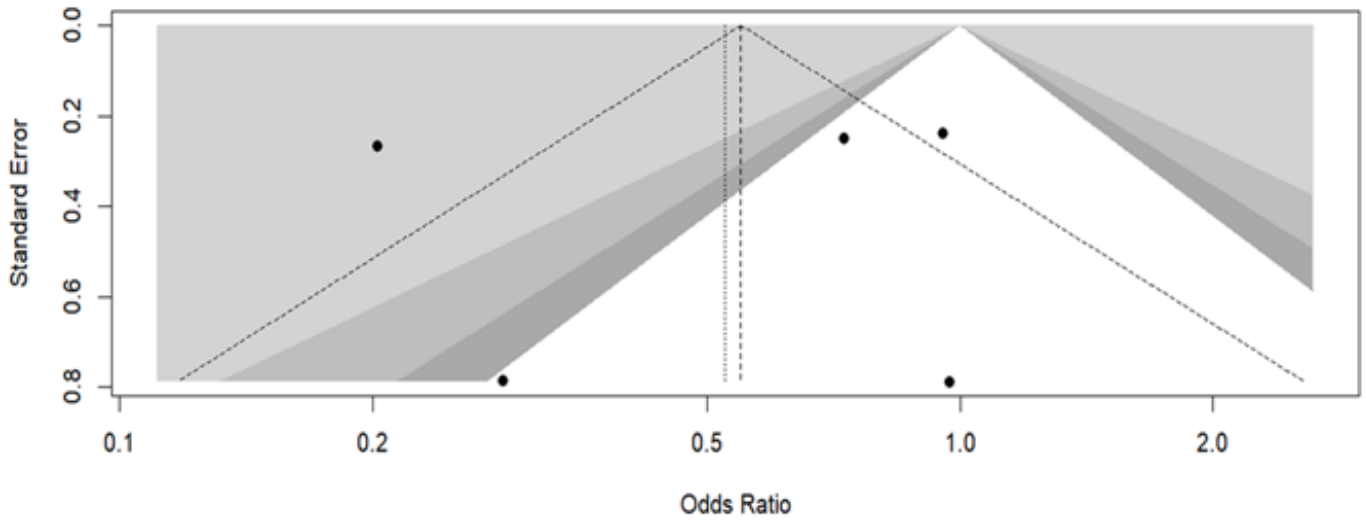

Figure 4: contour-enhanced funnel plot for the safety of the herbal remedies at 90% 95% and 99% confidence intervals for the treatment of sickle cell disease in Africa

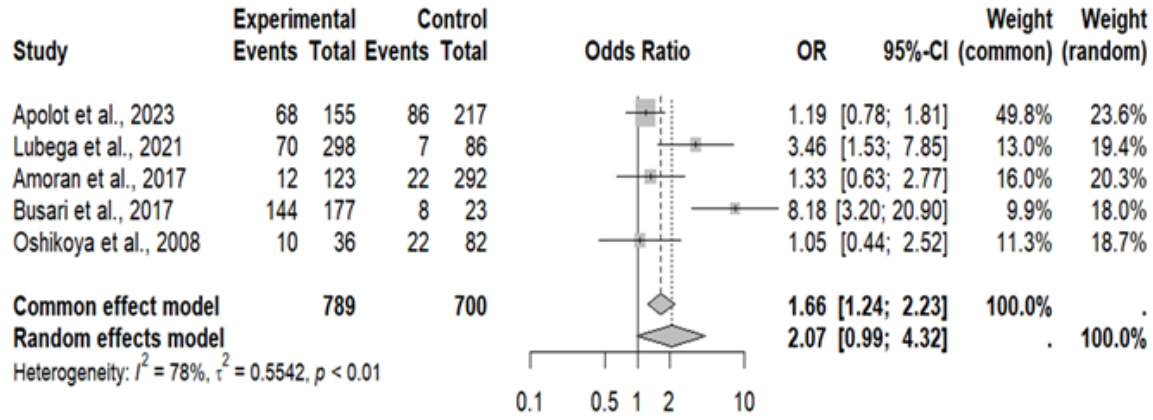

Figure 5: forest plot of the efficacy of herbal remedies for the sickle cell disease treatment in Africa

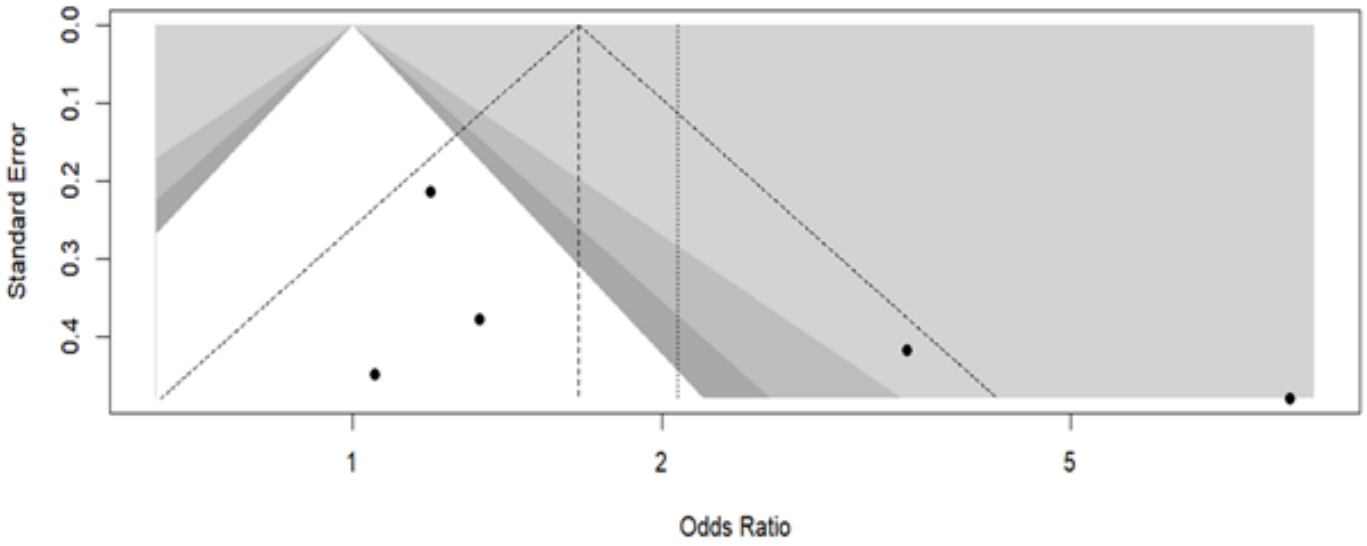

Figure 6: contour-enhanced funnel plot of the efficacy of the herbal remedies at 90%, 95% and 99% confidence intervals for the treatment of sickle cell in Africa