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Study Protocol

Preclinical efficacy of African medicinal plants used in the treatment of snakebite envenoming: a systematic review protocol

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Abstract

Background: Snakebite envenoming (SBE) is a high-priority, neglected, tropical disease that affects millions of people in developing countries annually. The only available standard drug used for the treatment of SBE is antisnake venom (ASV) which consists of immunoglobulins that have been purified from the plasma of animals hyper-immunized against snake venoms. The use of plants as alternatives for treatment of poisonous bites particularly snakebites is important in remote areas where there might be limited, or no access to hospitals and storage facilities for antivenom. The pharmacological activity of some of the medicinal plants used traditionally in the treatment of SBE have also been scientifically validated.

Method: A systematic review will be conducted according to the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies checklist for study quality in animal/*in vivo* studies. The tool will be modified and validated to assess *in vitro* models and studies that combine *in vivo* and *in vitro* studies. The systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. English published articles on African medicinal plants used in the treatment of snakebite envenoming will be searched in Medline, Embase, and Scopus from 2000 to 2021.

Dissemination: The findings of the study will be communicated through publication in peer-reviewed journal and presentation at scientific conferences. Medicinal plants have been important sources for the development of many effective drugs currently available in orthodox medicine. Botanically derived medicines have played a major role in human societies throughout history. Plants components used in traditional medicine gained much attention by many toxinologists as a tool for designing potent antidotes against snake envenoming. Our systematic review will provide a synthesis of the literature on the efficacy of these medicinal plants. We will also appraise the prospects of African medicinal plants with pharmacologically demonstrated activity against snakebite and envenoming.

Keywords: Antivenom, snakebite, medicinal plant, traditional, Africa

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Introduction

Snakebite envenoming (SBE) is a high-priority, but relatively neglected, tropical disease that affects millions of people in developing countries annually.[1–3] The problem has particularly reached a disturbing level in sub-Saharan Africa. SBE results in serious morbidity and mortality especially in poor communities where access to appropriate treatment is often lacking.[2] About 5.4 million people are bitten by snakes annually with 2.7 million clinical cases. The global death toll ranges from 81,000 to 138,000 annually.[4] Four

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families of venomous snakes are found in sub-Saharan; Viperidae, Elapidae, Colubridae, and Actraspididae.[5] The only available standard drug used in the treatment of SBE is antisnake venom (ASV) which consists of immunoglobulins, or immunoglobulin fragments, purified from the plasma of animals hyper-immunized against snake venoms.[1] Poor access to health services and scarcity of ASV in African settings have often led to poor outcomes and considerable morbidity and mortality.[6] Furthermore, the cost of orthodox ASV have led some victims to seek for alternative care from the traditional snake charmers who mostly utilized medicinal plants to treat victims. Although many African traditional snake charmers have ineffectively used myths and superstitions in managing snakebite, there have been many anecdotal reports that traditional healers still utilized some medicinal plants in the treatment of SBE.

Traditional medicine refers to the knowledge, skills, and practices based on the theories, beliefs, and experiences used in the maintenance of health and in the prevention, diagnosis, improvement, or treatment of physical and mental illness. Herbal treatments using medicinal plants are the most popular form of traditional medicine and 70–80% of the African Region has used a form as primary health care.[4] Medicinal plants have been used for the treatment of many diseases in Africa and around the globe. They have also been the most productive sources for the development of many effective drugs currently available in orthodox medicine. Botanically derived medicines have played a major role in human societies throughout history.[7] Medicinal plants have been discovered and used in traditional medicine practices since prehistoric times. Plants synthesize hundreds of chemical compounds for various functions including defense against insects, fungi, diseases and herbivorous mammals. Numerous phytochemicals with potential or established biological activity have been identified. The phytochemical constituents and pharmacological actions of many plants that have medicinal potential remain relatively unassessed by rigorous scientific research to define efficacy and safety. Medicinal plants still remain one of the bases for the development of modern drugs. They have also been used for years in daily life to treat diseases worldwide.[8]

The use of plants as alternatives for treatment of poisonous bites particularly snakebites is important in remote areas where there is limited or no access to hospitals and storage facilities for antivenom. Medicinal plants are popularly used in the treatment of snakebites and envenoming across the globe especially in Africa and Asia.[9] The pharmacological activity of some of the medicinal plants used traditionally in the treatment of SBE have been scientifically validated.[10,11] Compounds have been isolated with biological activity against snake venom.[12,13] Some medicinal plants in Africa and Asia have been preclinically evaluated, and observed to possess antivenom activities.[14] The investigated antivenom properties in the preliminary investigation of antivenom properties by some medicinal plants can provide strategic solutions to this neglected disease.[6] Sub-Saharan Africa is facing a snakebite crisis due to the poor healthcare system and lack of effective ASV among others. Fortunately, the rich flora collection of Africa provides a potential resource for researchers/traditional healers/government to harness, research, and use to proffer remedy to the current crisis. The use of components from medicinal plants as a tool for the design of potent antidotes against SBE has gained much attention from toxinologists worldwide.[15] Our systematic review will evaluate and appraise the prospects of available African medicinal plants with demonstrated activity against snakebite and envenoming.

Aim of the study

The aim of the study is to evaluate the efficacy of African medicinal plants used in the treatment of SBE.

Specific objectives

1. To systematically review the preclinical efficacy of African medicinal plants used in the treatment of SBE in *in vitro* rodent's models.
2. To systematically review the preclinical efficacy of African medicinal plants used in the treatment of SBE in animal/*in vivo* studies.
3. To review the prospects and challenges of African medicinal plants used in the treatment of SBE.

Methods

The systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] The CAMARADES animal study checklist for study quality will be used to assess the included *in vivo* studies and the same tool will be modified to assess *in vitro* models and studies that combine *in vivo* and *in vitro* studies.[17]

Databases to be searched

English published articles will be searched in PubMed, Embase, Scopus, and ScienceDirect from 2000 to May, 2021.

Search strategy

Medline via *PubMed.* ('herbal medicine'(MeSH Terms) OR 'plants, medicinal'(MeSH Terms) OR 'plant extracts'(MeSH Terms) OR 'teas, herbal'(MeSH Terms) OR 'medicine, traditional'(MeSH Terms) OR 'medicine, african traditional'(MeSH Terms) OR 'phytotherapy'(MeSH Terms) OR 'pharmacognosy'(MeSH Terms) OR 'ethnobotany'(MeSH Terms) OR 'ethnopharmacology'(MeSH Terms) OR 'materia medica'(MeSH Terms) OR 'homeopathy'(MeSH Terms) OR 'complementary therapies'(MeSH Terms) OR 'spiritual therapies'(MeSH Terms) OR 'naturopathy'(MeSH Terms) OR 'acupuncture therapy'(MeSH Terms) OR 'cupping therapy'(MeSH Terms) OR 'mind body therapies'(MeSH Terms) OR 'herbal plant*'(Title/Abstract) OR 'herb*'(Title/Abstract) AND ('snakes'(MeSH Terms) OR 'elapidae'(MeSH Terms) OR 'viperidae'(MeSH Terms) OR 'crotalinae'(MeSH Terms) OR 'naja'(MeSH Terms) OR 'naja naja'(MeSH Terms) OR 'naja haje'(MeSH Terms) OR 'snake bites'(MeSH Terms) OR 'snake venoms'(MeSH Terms) OR 'viper venoms'(MeSH Terms) OR 'crotalid venoms'(MeSH Terms) OR 'elapid venoms'(MeSH Terms) OR 'crotalid venoms'(MeSH Terms) OR 'elapid venoms'(MeSH Terms) OR 'antivenins'(MeSH Terms) OR 'Echis'(Title/Abstract) OR 'Bitis'(Title/Abstract) OR 'Cobra'(Title/Abstract) OR 'snake antivenom*'(Title/Abstract) OR 'snake anti venom*'(Title/Abstract) OR 'snakebite*'(Title/Abstract) OR 'antisnake*'(Title/Abstract) OR 'anti snake*'(Title/Abstract) OR 'anti snake*'(Title/Abstract) OR 'snake antivenin*'(Title/Abstract) OR 'antivenom'(Title/Abstract) OR 'anti-venom'(Title/Abstract) OR 'snake antidote*'(Title/Abstract) AND ('Cameroon' (MeSH Terms) OR 'Chad'(MeSH Terms) OR 'Central African Republic'(MeSH Terms) OR 'Congo'(MeSH Terms) OR 'Democratic Republic of the Congo'(MeSH Terms) OR 'Equatorial Guinea'(MeSH Terms) OR 'Gabon'(MeSH Terms) OR 'Sao Tome and Principe'(MeSH Terms) OR 'Burundi'(MeSH Terms) OR 'Djibouti'(MeSH Terms) OR 'Eritrea'(MeSH Terms) OR 'Ethiopia'(MeSH Terms) OR 'Rwanda'(MeSH Terms) OR 'Somalia'(MeSH Terms) OR 'South Sudan'(MeSH Terms) OR 'Sudan'(MeSH Terms) OR 'Tanzania'(MeSH Terms) OR 'Uganda'(MeSH Terms) OR 'Angola'(MeSH Terms) OR 'Botswana'(MeSH Terms) OR 'Eswatini'(MeSH Terms) OR 'Lesotho'(MeSH Terms) OR 'Malawi'(MeSH Terms) OR 'Mozambique'(MeSH Terms) OR 'Namibia'(MeSH Terms) OR 'South Africa'(MeSH Terms) OR 'Zambia'(MeSH Terms) OR 'Zimbabwe'(MeSH Terms) OR 'Benin'(MeSH Terms) OR 'Burkina Faso'(MeSH Terms) OR 'Cabo Verde'(MeSH Terms) OR 'Cote d'Ivoire'(MeSH Terms) OR 'Gambia'(MeSH Terms) OR 'Ghana'(MeSH Terms) OR 'Guinea'(MeSH Terms) OR 'Guinea-Bissau'(MeSH Terms) OR 'Liberia'(MeSH Terms) OR 'Mali'(MeSH Terms) OR 'Niger'(MeSH Terms) OR 'Nigeria'(MeSH Terms) OR 'Senegal'(MeSH Terms) OR 'Sierra Leone'(MeSH Terms) OR 'Togo'(MeSH Terms) OR 'Egypt'(MeSH Terms) OR 'Algeria'(MeSH Terms) OR 'Libya'(MeSH Terms) OR 'Morocco'(MeSH Terms) OR 'Tunisia'(MeSH Terms) OR 'africa'(MeSH Terms) OR 'africa*'(Title/Abstract).

Scopus

(TITLE-ABS-KEY (herb* OR plant* OR extract* OR 'tradition* medicine*' OR 'tradition* remed*' OR 'alternat* medicine*' OR 'alternat* remed*' OR 'complementary therap*' OR 'complementary remed*' OR 'complementary medicine*' OR 'africa* medicine*' OR 'africa* therap*' OR 'africa* remed*' OR 'home medicine*' OR 'home therap*' OR 'home remed*' OR 'spirit* medicine*' OR 'spirit* therap*' OR 'spirit* remed*' OR ethnomedic* OR phytotherap* OR ethnotherap* OR phytochemi* OR pharmacognos* OR ethnobotan* OR ethnopharmacolog* OR 'materia medica' OR homeopath* OR naturopath* OR acupuncture* OR cupping* OR 'mind body therapies')) AND

(TITLE-ABS-KEY (snake* OR snakebite* OR elapid* OR viperid* OR crotalin* OR naja* OR echis OR bitis OR cobra OR snake-venom* OR viper-venom* OR crotalid-venom* OR elapid-venom* OR antivenin* OR anti-venin* OR 'anti venin*' OR snake-antivenom* OR antivenom* OR anti-venom* OR 'anti venom*' OR antis-nake* OR anti-snake* OR 'anti snake*' OR 'snake antidote*')) AND (TITLE-ABS-KEY (africa* OR cameroon OR chad OR 'Central African Republic' OR congo OR 'Equatorial Guinea' OR gabon OR principe OR burundi OR djibouti OR eritrea OR ethiopia OR rwanda OR somalia OR 'South Sudan' OR sudan OR tanzania OR uganda OR angola OR botswana OR eswatini OR lesotho OR malawi OR mozambique OR namibia OR 'South Africa' OR zambia OR zimbabwe OR benin OR 'Burkina Faso' OR 'Cabo Verde' OR 'Cote d'Ivoire' OR 'Ivory Coast' OR gambia OR ghana OR guinea OR 'Guinea-Bissau' OR liberia OR mali OR niger OR nigeria OR senegal OR 'Sierra Leone' OR togo OR egypt OR algeria OR libya OR morocco OR tunisia)).

EMBASE via *OVID*

(plant OR 'traditional medicine' OR 'complementary medicine' OR ethnopharmacology OR ethnomedicine OR phytomedicine) AND (snake OR snakebite OR anti-snake OR antivenin OR antivenom OR viperidae OR elapidae OR naja OR echis OR bitis) AND (africa).

Human disease modeled

Snakebite envenoming (SBE)

Inclusion and exclusion criteria

Inclusion criteria

1. Studies on venom-induced envenoming in rodents (mice, rabbit, and rat).
2. *In vitro* models of rodent's plasma/serum, whole blood, cell lines, and/or isolated issues/organs.
3. Data reporting *in vivo* biological activities of medicinal plants/extracts/constituents used in treatment of SBE or pathologies due to envenoming in Africa will be identified and included for analysis. The abstracts and full-text articles that pass this criterion will be considered.
4. Data reporting *in vitro* biological activities of medicinal plants/extracts/constituents used in treatment of SBE or pathologies due to envenoming in Africa, will be identified and included for analysis. The abstracts and full-text articles that pass this criterion will be considered.

Exclusion criteria (In order of Priority)

1. Non-animal studies.
2. Non-rodents' population.
3. Non-venom-induced studies.
4. Non-rodent's plasma, whole blood, cell lines, and/or isolated issues/organs.
5. Non-venom exposure.
6. Non-African medicinal plants.
7. Non-pharmacological effect.
8. Non-scientific claims.
9. Ethnobotanical surveys.
10. Unpublished data.
11. Ongoing research.

Comparator/control

Negative control group/sample (exposed control group/sample).

Outcome measure

In vivo and *in vitro* biological/pharmacological effect (pharmacological effect of the intervention among the exposed groups).

Procedure for study selection

Sixteen reviewers will be involved in data extraction from text, tables, graphs, and figures using an integrated online platform for performing systematic reviews of preclinical studies (http://syrf.org.uk). Discrepancies will be resolved by adhering to the study protocol and through adoption of recommendations from pre-selected experts in the research area. The exclusion criteria will strictly follow the order of priority.

Steps of study selection

1. Search title/abstract and/or full article in (PubMed, Scopus, Embase, and Institutional journals).
2. Removal of duplicates.
3. Record screening of title, abstract, and/or full-text articles.

4. Article excluded with reasons.
5. Article included with reasons.

Data to be extracted from the included studies

Data will be extracted from the design, animal/animal sample used, and the intervention of interest of each included study.

Study design

1. Control *vs* intervention group/samples.
2. Method of venom-induced pathology.
3. The region where the plants are used and/or collected.
4. *In vitro* assays such as immunoassays and chromatography of male/female rodent sample.

Animal

1. Male/female rodents (mice, rat, and rabbit).
2. Snake species (medically important snakes).
3. The region where the plants are used and/or collected.
4. Plasma/serum, cell lines, and isolated tissue of male and female rodents (mice, rat, and rabbit).

Intervention of interest

1. Medicinal plant and its origin.
2. Plant's part administered (crude plant extracts and phytochemical).
3. Route of plant administration.
4. Dose of plant part administered.
5. Concentration of plant extracts and phytochemical used.

Method for risk of bias and/or quality assessment

Discrepancies will be resolved through discussion among reviewers and adoption of recommendations from pre-selected experts in the research area.

SYRCLE's tool for assessing risk of bias

1. Plan approach for each tool.
2. Each reviewer will be introduced to the tool to be used.
3. Classify studies based on which tool to be used (*in vivo* or *in vitro*).
4. Assign number of reviewers for each tool (four reviewers per tool with equal number of studies to appraise).
5. Reviewers' appraisal will be done by describing and assigning level of risk as described by Hooijmans.[18]

Procedure for extended OHAT risk of bias rating tool for in vitro *studies*

1. Plan approach for each tool.
2. Each reviewer will be introduced to the tool to be used.
3. Classify studies based on which tool to be used (*in vivo* or *in vitro*).
4. Assign number of reviewers for each tool (four reviewers per tool with equal number of studies to appraise).
5. Reviewers' appraisal will be conducted by describing and assigning level of risk as described by Rooney.[19]

Study outcomes

Primary outcomes

1. Pharmacological activity (significance, mean difference, %).
2. Lethality (%).

Secondary outcomes

1. Neutralization of hemorrhagic effect (continuous data, mm, mean).
2. Neutralization of cytotoxic effect (continuous data, mm, mean).
3. Neutralization of neurologic effect (dichotomous data, %,).

Data synthesis and analysis

A narrative synthesis is planned as outlined below:

1. The studies will be grouped by intervention and study design.
2. The results will be described and summarized for all the included studies in a tabular form for easy comparison.
3. Exposed and controlled groups will be compared to evaluate efficacy.
4. The relationships within and between included studies will be uniformly described.

5. SYRCLES's risk of bias tool will be used to assesse the included *in vivo* studies.
6. SYRCLES's risk of bias tool will be modified using extended OHAT Risk of Bias Rating Tool for the included *in vitro* studies and studies that combine *in vivo* and *in vitro* studies.
7. CAMARADES checklist for study quality will be used to assess the included *in vivo* studies. The same tool will be modified to assess *in vitro* models and studies that combine *in vivo* and *in vitro* studies.

Dissemination

The findings of the study will be communicated through publication in peer-reviewed journal and presentation at scientific conferences.

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Author contributions

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Basheer Z.A. Chedi: Conceptualization; Methodology; Supervision; Writing – review & editing.

Conflict of interest statement

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Protocol registration

The protocol has been registered on PROSPERO with registration number CRD42021247711

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