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A systematic review of validated medicinal plants and their compounds as agents for the management of sickle cell disease

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 April 2024 and was last updated on 30 April 2024.

INTRODUCTION

Review question / Objective There is no evidence-based systematic review of medicinal plants and their compounds for sickle cell management. The objective was to document such plants and highlight species, genera, and some phytochemicals that could be primed for further research to develop novel anti-sickling medications.

Rationale Sickle cell disease (SCD) belongs to a group of inherited blood disorders or haemoglobinopathies. The disease affects about 50 million people throughout the world with a high prevalence in Africa and India. In countries such as Cameroon, Republic of Congo, Gabon, Ghana and Nigeria, the prevalence is between 20% to 30% while in some parts of Uganda it is as high as 45%. The only known medication for SCA is hydroxyurea (HU), which is recommended to reduce the number of painful episodes, reduce hospital stays and the requirement for blood transfusions. New medications such as Endari (L-glutamine oral powder) and Oxbryta (voxelotor) have been approved by the Food and Drug Administration (FDA) but are not cost effective. Stem cell transplant can cure SCD but requires a matched donor. The healthcare cost of the management of SCD patients is disproportionately high compared to the number of people afflicted by the disease. Most of the populace in Sub-Saharan Africa, where prevalence of the disease is very high, are mostly below the poverty line and unable to afford the high cost of treatment. People in this region have learnt to manage several diseases, including SCA. Thus, SCD management using medicinal plants is widespread, especially in developing countries. Several studies have validated medicinal plants used in traditional medicine for the management of sickle cell anaemia. However, there is no evidence-based systematic review of these medicinal plants and their compounds for sickle cell management. Such

a review will highlight plant families, genera and species with the potential to mitigate the treat posed by the disease for further research and drug discovery.

Condition being studied Sickle cell disease belongs to a group of inherited blood disorders or haemoglobinopathies. These are genetic blood diseases arising from the inheritance of mutant haemoglobin genes from both parents. Approximately 5% of the world's population carry genes for haemoglobin disorders, mainly, sickle-cell disease and thalassemia. Sickle cell anaemia (SCA), also known as drepanocytosis, haemoglobin S or SS disease, is the most important haemoglobinopathy worldwide according to the World Health Organization.

METHODS

Search strategy Research articles and general scientific publications regarding herbs or plant extracts that have significant effect in the treatment of sickle cell disease were looked-up in databases such as Google scholar, PubMed, Science direct, DOAJ, Open Alex, Wiley, AJOL, BioMed Central, JSTOR, and Scopus. A supplementary search was made in relevant institutional repositories and the bibliography section of papers included in the study. Search keywords used in this search included "anti-sickling and medicinal plants", "anti-sickling and herbs", "anti-sickling and plant extracts", "anti-sickle cell anaemia and medicinal plants", "anti-sickle cell anaemia and herbs" and "anti-sickle cell anaemia and plant extracts". The Boolean operators 'AND' and OR' were used to afford the intended results. There were 411 publications found and collected of which 53 were duplicates and 276 papers excluded as per the exclusion criteria. The search covered the period from January 2000 to December 2022.

Participant or population Medicinal plants are used by humans to treat sickle cell anaemia. There are no direct human participants in the reviews but the results are implied.

Intervention The review provides a list of medicinal plants which have been validated for the management of sickle cell disease. Thus providing an alternative to the use of these agents to conventional medicines for the management of the disease.

Comparator No applicable.

Study designs to be included Information extracted included experimental protocols describing in vitro or in vivo testing and other standardized assays that evaluated the effectiveness of the medicinal plant, herbs, plant extracts and compounds in treating sickle cell disease. The data collated from the publications included the scientific name of the plant, the plant family, method of extraction and solvent used, the testing method used to measure efficacy, the country of origin of the paper and the year of publication.

Eligibility criteria The scope of this review was restricted to scientific publications written in English language. Papers describing the pharmacological testing of plant materials for anti-sickling activities and published from 2000 to 2022 were included in the study. The study also covered articles describing the anti-sickling activities of plant derived compounds. Ethno-botanical surveys of anti-sickling medicinal plants without their pharmacological testing were also excluded. Additionally, papers which were not written in English, abstract only and had plant names in a local dialect with no scientific names.

Information sources Research articles and general scientific publications regarding herbs or plant extracts that have significant effect in the treatment of sickle cell disease were looked-up in databases such as Google scholar, PubMed, Science direct, DOAJ, Open Alex, Wiley, AJOL, BioMed Central, JSTOR, and Scopus.

Main outcome(s) The literature search covered 411 publications of which 82 were found to be eligible. More than half (53.65%) of the articles were published from 2016 to 2022. Anti-sickling research from Africa accounted for 86.58% of the publications, with more than half coming from Nigeria, 12.20% from Asia and only 1.22% from Europe. A total of 51 anti-sickling plant families containing 117 species were documented. The family Fabaceae recorded the highest number of species (ten) and genera (nine). Other dominant families included Euphorbiaceae (nine species and six genera), Annonaceae (eight species and six genera), Apocynaceae (five species and five genera), Combretaceae (five species and three genera), Phyllantaceae (five species and four genra), Rubiaceae (five species and five genera), Rutaceae (four species from one genus) and Apocynaceae (five species and five genera) (Figure 2). The most reported species were Carica papaya L (n=5), Terminalia catappa L (n= 3) and Annona muricata L. (n=3) whereas Zanthoxylum (n=4), Terminalia (n=3) and Ocimum (n=3) dominated the

list of plant genera with anti-sickling properties. Benzoic acid derivatives, butyl stearate, ellagic acid derivatives and some pentacyclic triterpenoids were the only plant-derived compounds validated for anti-sickling activities.

Data management The guidelines for the selection and inclusion of articles described by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). All articles from the search were kept in folders and duplicates removed a nd kept in separate folders. After screening for eligibility, articles not included in the analysis were also put in a separate folder. The relevant information were extracted onto an excel sheet, organized into sections.

Quality assessment / Risk of bias analysis Two people performed the data extraction and comparisons were made. Where there was a difference, we discussed and resolved.

Strategy of data synthesis Given the research question or study aims, all data extracted onto the excel sheet were analysised based on sections. Evidence of plant use for sickle cell were obtained, protocols used and isolated compounds tested were identified.Knowledge gaps were also identified.

Subgroup analysis The data was split into sections and in some cases sub-subsections were created and analysed.

Sensitivity analysis The research topic and parameters extracted were direct and straight to the point. Nevertheless, a repeat analysis of the data was done to avoid to ensure acceptability of the results.

Language restriction No.

Country(ies) involved Ghana.

Keywords Haemoglobinopathies; medicinal plants: anti-sickling assay; anaemia; Zanthoxylum species; sickle cell.

Dissemination plans Through my institutional research platforms, professional platforms, social media handles, and presentations at relevant meetings/workshops and conferences.

Contributions of each author

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