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# Reviewing and Prospecting Anthelmintic Compounds Derived from Medicinal Plants in Africa

Jonathan Jatoi, Christian Agrye
Kwame Nkrumah University of Science and Technology: Kumasi, Ashanti, GH

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## Abstract

Soil-transmitted helminthiasis affects more than 1.5 billion people globally and largely remains a sanitary problem in Africa. These infections place a huge economic burden on poor countries and affect livestock production, causing substantial economic losses and poor animal health. The emergence of anthelmintic resistance, especially in livestock, and the potential for its widespread in humans create a need for the development of alternative therapies. Medicinal plants play a significant role in the management of parasitic diseases in humans and livestock, especially in Africa. This report reviews anthelmintic studies that have been conducted on medicinal plants growing in Africa and published within the past two decades. A search was made in various electronic databases, and only full articles in English were included in the review. Reports show that aqueous and hydroalcoholic extracts and polar fractions obtained from these crude extracts form the predominant (80%) form of the extracts studied. Medicinal plants, extracts, and compounds with different chemical groups have been studied for their anthelmintic potential. Polyphenols and terpenoids are the most reported groups. More than 64% of the studies employed in vitro assays against parasitic and nonparasitic nematode models. Egg hatch inhibition, larval migration inhibition, and paralysis are the common parameters assessed in vitro. About 72% of in vivo models involved small ruminants, 15% rodents, and 5% chicken. Egg and worm burden are the main factors assessed in vivo. There were no reports on interventions in humans cited within the period under consideration. Also, few reports have investigated the potential of combining plant extracts with common anthelmintic drugs. This review reveals the huge potential of African medicinal plants as sources of anthelmintic agents and the dire need for in-depth clinical studies of extracts, fractions, and compounds from African plants as anthelmintic agents in livestock, companion animals, and humans.

## 1. Introduction

Parasitic worms affect more than one-quarter of the world's population, with soil-transmitted helminthiases (STH) accounting for about 1.5 billion infections [1, 2]. STH is one of the neglected tropical diseases (NTDs) that affects mainly people living in regions of high poverty, without adequate sanitation, and in close contact with infectious vectors, domestic animals, and livestock [2, 3]. They occur globally in the tropics and subtropics, including the Americas, Asia, and sub-Saharan Africa. These areas are more impacted because of the low levels of development [2, 4].

Helminth infection is largely a sanitary problem and is associated with the human-animal food chain. Parasite eggs present in human faeces contaminate the soil where they embryonate and are taken back into the intestinal tract through poorly treated drinking water and foods [5]. This creates a vicious cycle of recurrent infections that is often difficult to break or interrupt [3, 6].

Although helminthiases have a low fatality rate, they have a huge impact on human health and livestock production. The severity of symptoms in humans depends on the worm burden and whether monospecific or mixed infections are involved [2, 7]. Whilst children constitute the most vulnerable group to worm infestation, pregnant women also suffer impaired immunity and a lower quality of life [5, 8–10].

Based on the location of the adult parasite in the body, helminthiases may clinically present as intestinal (whipworms, intestinal roundworms, and hookworms), or tissue (trematodes, hydatid tapeworms, and tissue roundworms) parasites [5, 11]. The most common and widespread intestinal nematodes in humans include *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, *Trichuris trichiura*, and *Strongyloides stercoralis*, which have been classified as soil-transmitted helminthiases [3, 12]. Mild symptoms include abdominal pain, nausea, diarrhoea, and loss of appetite, and in children, severe cases may lead to anaemia, eosinophilia, stunted growth, malnutrition, pneumonia, and poor physical and cognitive development [3, 13]. High-intensity infections could result in intestinal obstruction requiring surgery and death in cases of *Strongyloides stercoralis* [14].

Unlike for some viral and bacterial diseases, there are currently no vaccines developed for human intestinal parasites [5, 15, 16]. In livestock, however, the first vaccine (Barbervax®) against *H. contortus*, which is derived from an intestinal surface antigen of the nematode, has proven to be a sustainable control measure in small ruminants [17]. Control measures mainly include periodic deworming, health education, and improvements in environmental sanitation. Seasonal chemotherapy with synthetic anthelmintics remains the primary measure to eliminate or reduce infecting helminths. Health education helps to prevent reinfection, while improved sanitary conditions reduce egg transfer to soil [14].

Morbidity due to helminthiases has been greatly reduced by the annual or biannual mass drug administration (MDA) in vulnerable populations. The two benzimidazole drugs, mebendazole and albendazole, are the core agents recommended by the World Health Organization (WHO) for MDA in children of school age. Both drugs are effective, cheap, easy to administer, and have been used in large populations for several years with minor side effects [14]. Other classes of anthelmintic drugs available include macrocyclic lactones, imidazothiazoles, tetrahydropyrimidines, and amino-acetonitrile derivatives. Other drugs, including levamisole, pyrantel pamoate, niclosamide, ivermectin, and piperazine, have contributed immensely to tackling livestock and human parasites [18].

The increase in cost, availability, continual reinfection, emergence of drug-resistant parasites, adverse events associated with population-wide drug use [9, 17, 19], and lack of coverage for other infectious agents like *Strongyloides* have become major drawbacks to the success of anthelmintic chemotherapy [20]. These threats have spurred the quest to discover and develop new, innovative, sustainable, effective, safe, alternative, and complementary treatment options, mostly from natural products [21–24].

In Africa, about 80% of the population largely depend on traditional remedies for their primary healthcare needs [25–27]. Compared to orthodox medicines, these remedies are relatively accessible and cheaper, perceived to be safe and effective, and form part of folkloric practices [22, 24, 28]. Plants form the larger part of these traditional remedies and have historically been used in treating internal parasites and other diseases in humans and livestock [15, 29, 30]. They constitute a viable source of chemically diverse molecules with broad-spectrum activity and can be a ready means to combat parasite resistance. From January 1981 to September 2019, 71 new approved drugs were entirely derived from natural products, 14 as natural botanicals, and 356 as semisynthetic derivatives of natural molecules [31]. However, there is currently no anthelmintic drug product approved that has been developed from plant sources [18].

Even though the chemical constituents and mechanisms by which medicinal plants elicit the observed activities are less known [28, 32], technological advancement has reignited research using in vitro and in

vivo assays to evaluate ethnopharmacological claims and, where possible, identify such chemical entities and their mechanisms [22, 28].

This review is unique in the sense that it gathers information on anthelmintic extracts, fractions, and compounds from African medicinal plants. It seeks to reveal the potential of African medicinal plants as sources of new anthelmintic molecules and alternative therapies against helminthiases.

Whereas the African continent has a huge natural resource pool that is widely used by local people, especially indigenous people, for the management of many disease conditions, the continent remains one of the hardest hits by intestinal parasites [2]. There is increasing research into natural products, especially medicinal plants, as sources of new antiparasitic agents. Despite efforts to gather the library of these plant products, be they extracts, fractions, or purified compounds [7, 23, 33], those available from African medicinal plants are scattered and limited to certain geographical regions. This review, therefore, sought to expand this pool of information and to create a clear picture of the situation as far as studies of anthelmintic agents from African medicinal plants are concerned. Here, we elaborate on the various studies that have been conducted on medicinal plants native to Africa and espoused on the very promising plant families and species.

## 1.1. Methodology

### 1.1.1. Inclusion and Exclusion Criteria

For the scope of this review, full-text articles published in credible peer-reviewed journals, publishers, and repositories (see below) whose studies focused on the anthelmintic activities of medicinal plants that grow in Africa were included. Only articles written in English and published between January 2002 and December 2021 were included, no matter where the study was conducted.

Articles written before 2001 and after 2021 were excluded. Articles that focused on extracts, fractions, and/or compounds isolated from medicinal plants not growing in Africa were also excluded. Even though this review is extensive, it is not a systematic review. The review also significantly focused on gastrointestinal nematode-related studies than other types of helminthiases.

### 1.1.2. Literature Search and Data Extraction

Articles were identified through literature searches in relevant electronic databases and search engines, including Scopus, Science Direct, Academic Journals, African Journals Online (AJOL), HINARI, BioMed Central, Google Scholar, JSTOR, and PubMed. Bibliographies of included articles were further searched, and pertinent, relevant information retrieved in primary searches was added. This search was conducted between April 2020 and April 2022.

Articles that were retrieved were independently screened by at least three authors, and those that met the inclusion criteria were selected for review.

Data were often obtained from relevant portions of the articles, including the “materials and methods” and “results” sections. The extraction focused on the botanical source of plant material, the nature of extracts, fractions, or compounds, and the type of assay employed, including in vitro and in vivo studies. The relevant measures of efficacy in the test system, including $IC_{50}$, $EC_{50}$, $LC_{50}$, and $LD_{50}$, were used to assess the anthelmintic potential of the study samples. Mendeley Desktop (version 1.19.4, copyright 2008–2020, Mendeley Ltd.) was used to manage the citations.

The botanical identities of plants and their habitats in Africa were verified against information from https://www.worldfloraonline.org/search (formerly https://www.theplantlist.org) and https://plants.jstor.org/plants/browse.

## 2. Anthelmintic Resistance in Humans and Livestock

Parasite susceptibility to the existing anthelmintic drugs continues to rapidly decline, leading to the emergence of drug-resistant parasites. Several studies have reported the development and spread of resistance to all major classes of anthelmintics [34–36], especially in livestock and, to a lesser extent, in companion animals and humans [9, 37]. The main contributing factors to drug resistance include selective pressure induced by high treatment frequencies, single-drug regimens, preventive mass treatments, inadequate dosing, indiscriminate use, and overreliance on synthetic drugs to control helminthiases [18, 34, 38].

High-frequency preventive chemotherapy in humans and livestock, as a result of the high disease burden and limited number of anthelmintics, causes a reduction in worm refugia-enhancing mutations and resistance development [5, 21, 39]. Prolonged use of single drugs, for example, the use of ivermectin for Onchocerciasis control in West Africa and praziquantel against Schistosomiasis in Egypt, has been associated with widespread resistance [34].

The development and spread of drug-resistant traits at the molecular level have been well investigated in the model organism *C. elegans* [40] and the barber's pole worm (*H. contortus*) [41]. Mutations in genes coding for drug receptor sites or the expression of genes involved in drug efflux, detoxification, or amphidial drug uptake have for instance been reported as possible causes of drug resistance [42, 43]. Resistance to the benzimidazoles in trichostrongylid nematodes in ruminants has been ascribed to mutations in the isotype 1 $\beta$-tubulin gene (E198A, E198L, F167Y, and F200Y) [44–46].

Nematodes, generally upon hatching, undergo multiple larval developmental stages into adult worms [5], and this multistage cycle poses a challenge to drugs that target just a few stages. Broad-spectrum activity against egg hatching, larval metamorphosis, and adult worms is therefore an ideal requirement for anthelmintic agents [7].

The use of plant extracts may significantly delay and reduce the spread of resistance among parasite populations [47, 48]. These multicomponent systems with natural products from very different classes could interact with multiple developmental stages, help reduce natural selection pressures, and delay resistance development, which are typically found in such multitarget systems [49–51]. Selective treatment of individuals, multidrug therapy, and environmental parasite control strategies slow down the emergence of selective resistance alleles [38].

## Conclusion

The World Health Organization's 2030 targets for STH can only be achieved with renewed investments in new and effective drugs. African medicinal plants will serve as a useful source of remedies for integrated parasite control, along with other measures such as education and the provision of sanitation facilities to at-risk populations.

The foregoing data validate the claims that African medicinal plants have huge potential for the discovery and development of new, innovative, and alternative anthelmintic agents. The majority of reports and studies evaluated extracts of plants, with a few isolated compounds also characterized. Even though in

vivo animal studies abound, 78% of the studies reported in vitro activities against parasitic nematodes. There are no reports available on clinical investigations of extracts or purified compounds in humans, nor have any commercial products been reported or evaluated for their effectiveness. Therefore, clinical evaluation of these plant products and mechanistic studies, especially on isolated compounds, will advance the goal of identifying and developing drug candidates from plant sources. [256].

## Abbreviations

DCM: Dichloromethane

$EC_{50}$: Half maximal effective concentration

$ED_{50}$: Half maximal effective dose

EHIA: Egg hatch inhibition assay

EPG: Egg per gram

FEC: Faecal egg count

FECR: Faecal egg count reduction

GIN: Gastrointestinal nematodes

$IC_{50}$: Half maximal inhibitory concentration

$LC_{50}$: Half maximal lethal concentration

$LD_{50}$: Half maximal lethal dose

LMIA: Larval migration inhibition assay

MDA: Mass drug administration

QSAR: Quantitative structure-activity relations studies

STH: Soil-transmitted helminthiases

WHO: World Health Organization.

## Data Availability

No data were used to support this study.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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