Chapter

The Ghanaian Flora as a Potential Source of Anthelmintic and Anti-Schistosomal Agents

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Abstract

Parasitic infections including schistosomiasis and soil transmitted helminthiasis are the most commonly encountered Neglected Tropical Diseases (NTDs) in the world. These diseases remain a major public health concern affecting millions of people especially those living in poor regions where access to effective conventional health care is a challenge. Interventions to control these infections in endemic areas have not been successful due to the high cost of drugs, limited availability as well as inequity of access to preventive chemotherapies. Another problem is the development resistance to the limited number of recommended medications due to their intensive use in both human and live-stock. There is an increasing awareness of the potential of natural products as chemotherapeutic agents to combat parasitic infections. Natural products may offer an unlimited source of chemically diverse drug molecules which may be safe, efficient, less toxic, less expensive and readily available for use especially in low-income countries. The Ghanaian flora provides such a ready source for new therapeutic interventions for the local population. Several researches have provided evidence of the anti-parasitic activity of Ghanaian medicinal plants. This chapter provides a review with special focus on medicinal plants collected from Ghana with anthelmintic and anti-schistosomal activity. Evidence of pharmacological activities of crude extracts, fractions and bioactive phytoconstituents as well as possible mechanisms of action where investigated are discussed.

Keywords: schistosomiasis, worms, parasite, helminth, Ghana, herbal medicine

1. Introduction

Neglected tropical diseases (NTDs) include a collection of chronic, disabling, and physically disfiguring infectious diseases that usually affect dwellers of poor rural populations in tropical and sub-tropical countries of the world [1]. Apart from their negative impact on the health of victims, NTDs exert an immense socio-economic burden on the society as a result of the social stigma and physical disabilities associated with them. These interrelated negative outcomes perpetuate a cycle of poverty and unproductivity resulting in a consistent decline in economic growth [2]. As a major element of the Millennium Development Goals (MDGs), much effort is being put in for the elimination of the NTDs [3].

Among the NTDs, helminth infections especially soil-transmitted helminthiasis (STHs) and schistosomiasis are among the most prevalent afflictions of humans [4]. About 2 billion people are estimated to suffer from helminth infections worldwide, out of whom 300 million suffer from severe morbidity [5]. The negative impact of helminth infections on human growth and development (including cognitive development in childhood and nutritional status), pregnancy and work performance cannot be overemphasized. Though considered as acute health problems in some developed parts of the world, chronic parasitic infections are common and recurrent in poor communities and usually result in long-lasting complications making them a significant health threat to the populations who are continuously at risk for infection [6].

Over the years, many highly effective chemotherapeutic agents have been developed for treating helminth infections. Unfortunately in the setting of rural poverty where these diseases are mostly prevalent, access to healthcare facilities and the cost of medications are a challenge [7, 8]. Additionally, environmental factors and unavoidable domestic or occupational exposures, strongly favor the process of re-infection even after a successful therapy [9, 10]. Given that these infections also require lengthy treatment regimens with related costs which cannot be afforded by the affected victims, many patients seek for alternative treatment options especially the use of herbal medicines which are readily available and less expensive [9, 11].

Herbal extracts have been used in traditional medicines since ancient times for the effective treatment of human diseases [12]. Ethnobotanical studies in various regions of the world have documented medicinal plants used for the treatment of various parasitic infections. Scientific investigations of selected plants have also revealed remarkable activity of medicinal plants against specific human parasites [13, 14]. In Ghana, numerous medicinal plants play an important role in the healthcare system of rural communities. The Ghanaian flora provides a ready source for new therapeutic interventions for the local population [15–17]. This chapter provides a review with special focus on medicinal plants collected from Ghana with anthelmintic and anti-schistosomal activity.

1.1 Soil transmitted helminthiasis (STH)-the disease burden and current chemotherapy

Soil transmitted helminth (STH) infections are a group of infections which are acquired by the ingestion of, or contact with, soil containing infectious worm eggs or larvae [18]. STHs have been reported as the most common parasitic infections encountered in humans with an estimation of more than 1 billion people infected with at least one or more helminth parasites. They constitute an important global health challenge in resource deprived parts of the world and are prevalent in areas of poor sanitary conditions [19].

The main species of clinical importance are the intestinal roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and the hookworms (*Necator americanus* and *Ancylostoma duodenale*) [18]. Common symptoms of intestinal helminthiasis include abdominal pains, nausea, itching and diarrhea and in severe cases, anemia, pneumonia, eosinophilia and malnutrition. School-aged children and preschool children are the most vulnerable group who harbor the greatest numbers of intestinal worms. As a result, they experience growth stunting and diminished physical fitness as well as impaired memory and cognition [20]. Although helminth infections are not known to be lethal as compared to other infections, they are recurrent among poor people and pose an enormous impact on the socio-economic status of the society affected [21].

Anthelmintics are a group of antiparasitic drugs that expel worms and other internal parasites out of the body by either stunting or killing them. For the treatment of STHs, the benzimidazoles specifically albendazole and mebendazole are the current treatment drugs of choice [19]. The main challenge with these anthelminthics is the development of resistance due to the intensive use of drugs in both human and live-stock [22]. With few new drugs evolving against helminth infections over the years, the fight against these parasites could become a losing battle, thus the need to search for new alternatives.

1.2 Schistosomiasis—the disease burden and current chemotherapy

Schistosomiasis, widely known as bilharzia, is caused by infection with blood flukes of the genus *Schistosoma* which is transmitted through contact with infected fresh-water snail vectors. Schistosomiasis is reported to be the 2nd leading endemic parasitic disease in the world after malaria. The disease affects more than 240 million people in tropical and subtropical areas with about 90% cases reported from sub Saharan Africa [23, 24].

Five species of the schistosome parasite namely: *Schistosoma mansoni*, *Schistosoma haematobium*, *Schisosoma japonicum*, *Schistosoma mekongi*, and *Schistosoma intercalatum* usually affect humans [25]. In sub-Saharan Africa the main burden of disease is usually attributed to *S. mansoni* and *S. haematobium* which cause intestinal and urinary schistosomiasis respectively [10]. The infection is mainly characterized by painful bloody urination in urinary schistosomiasis or blood stained diarrhea in intestinal schistosomiasis. Long term effects include liver fibrosis, renal failure, cancer of the bladder, infertility and increased risk of contracting HIV. In children, schistosomiasis results in malnutrition, growth retardation, cognitive defects and chronic anemia [6, 26].

For the eradication of schistosomiasis, control programmes have been based on preventive chemotherapy. The WHO endorsed and advocated for mass drug administration (MDA) especially among school children utilizing a single oral dose of 40 mg/kg praziquantel [27]. Unfortunately, the unavailability of the drugs due to cost, poor drug coverage, inequity of access to chemotherapy and non-compliance to therapy due to adverse side effects have impeded the progress of this approach [7, 28]. The expansion of preventive chemotherapy has also raised concerns about the potential development of resistance to praziquantel (PZQ) which remains the only commercially readily available drug for the control of schistosomiasis [29]. Some studies have reported low cure rates of PZQ attributing this to possible mutation of the schistosome parasite as well as inactivity of PZQ against early stages of the worms [30, 31]. It is thus not a satisfactory situation to have only one single effective treatment. Ideally, other anti-schistosome drugs should be developed so that the classical strategy of avoiding development of resistance could be followed.

1.3 Methods used in this review for identifying medicinal plants with anthelminthic and anti-schistosomal activities

Reported anthelmintic and anti-schistosomal activities of medicinal plants collected from various parts of Ghana were obtained from electronic databases including PubMed, SciFinder and Google Scholar. The inclusion criteria were that: (i) plants should be used in Ghanaian traditional medicine for treatment of worm infestations or expulsion of worms and schistosomiasis (urinary and intestinal) or other condition characterized by the symptoms of the above diseases (ii) plant should have been investigated for anthelmintic or anti-schistosomal (cercaridial)

activity using one or more validated *in vitro* or *in vivo* models (iii) the right botanical names, plant parts used, types of extracts prepared, active constituents and mechanisms of action if investigated were mentioned. Consideration was also given to plants with significant activity differences with reference to control groups.

2. Plants with anthelminthic activity identified from Ghana

The anthelmintic activity of plant extracts was mostly studied by evaluating their effect on worms after direct exposure for a period of time. Earthworms including *Pheretima posthuma*, *Lumbricus terrestris*, *Eudrilus eugeniae* and *Caenorhabditis elegans* were employed as target organisms due to their anatomical and physiological similarity to the human intestinal round worm, ease of availability, adaptability to laboratory conditions and ease of handling.

2.1 *Alcornea cordifolia* (Schumach & Thonn) Müll. Arg. Euphorbiaceae

Alchornea cordifolia, commonly called the Christmas bush is a straggling, laxly branched evergreen dioecious shrub growing up to about 8 m tall. It is locally known as '*agyama*' in the Ghanaian Akan language and an essential medicinal plant in traditional medicine. Various parts of the plant are used to treat jaundice, diarrhea, rheumatic pains, malaria, fever, wounds, colds, asthma, amoebic dysentery and worm infections. Other literatures report its use in the treatment of urinary and gastrointestinal infections, leprosy, yaws, filariasis as an antidote to snake venom [32].

The anthelminthic potency of the petroleum ether, chloroform and methanol extracts of *A. cordifolia* leaves were investigated by evaluating its effect on the gross motility and mortality of earthworms (*Pheretima posthuma*). The extracts displayed significant ($p < 0.001$) concentration-dependent anthelminthic activity at concentration range of 0.75 to 12.00 mg/mL. At the highest concentration, worm paralysis was effectuated between 10 and 26 mins whiles death occurred between 57 to 93 min. The effect of the extracts in reducing the paralysis and death times of the worms was significantly higher than the effect on albendazole-treated worms [33].

2.2 *Alstonei boonei* De Wild (Apocynaceae)

Alstonia boonei is an indigenous African tree mostly distributed in the evergreen rain forest of tropical West Africa. In Ghana it is locally called '*Nyame dua*' meaning God's tree in the Akan language. In the western coastal regions of Africa, this plant is well known for its extensive use in traditional medicine for treating rheumatism, general body pains, worm infestation and diabetes. A cold infusion of the fresh or dried bark is used as a vermifuge to expel intestinal worms and other intestinal parasites in children [34].

The methanol extracts (50–150 mg/mL) of the stem bark and roots of *A. boonei* were investigated *in vitro* for anthelmintic effects against the adult Indian earthworm, *Pheretima posthuma* by direct exposure of worms to the extracts. The stem bark extract exhibited a concentration dependent anthelmintic activity causing paralysis of worms within 15–55 mins and death within approximately 100 mins which was significant ($p < 0.01$) compared to the untreated group. The stem bark extract had a better anthelmintic effect than the root bark [35].

In another study, the aqueous and ethanolic stem bark extracts (50–200 mg/mL) of *A. boonei* demonstrated significant anthelmintic activity against *Lubricus terretris*.

While worms in the untreated group saw no paralysis or death after 120 mins of exposure, the extract-treated worms were paralyzed within 8–16 minutes of exposure and died within approximately 21–27 minutes of exposure [36].

2.3 *Azadirachta indica* A. Juss. (Meliaceae)

Azadirachta indica, commonly known as neem, is a fast-growing and long lived evergreen tree which grows up to about 15 m tall with long, spreading branches that form a dense, large rounded crown. The plant is a multipurpose medicinal plant which also provides food and timber and is widely distributed in several regions of Asia and Africa. It is well known for its insecticidal and insect-repelling property. Various parts of the plants are reported to be used for the treatment of many ailments in traditional medicine including malaria, fever, upper respiratory tract infections, wound healing, sexually transmitted infections and skin diseases [37].

The anthelmintic activity of the ethanolic extract of *A. indica* seeds was investigated *in vivo* using albino rats (*Rattus norvegicus*) infected with helminth species including: *Hymenolepsis diminuta*, *Enterbius vermicularis* and hookworm. The rats were treated with the alcoholic extracts (20–60%) over a 3-week period and fecal samples were examined for eggs. The extract treated groups showed declining levels of egg count by the 3rd week and complete elimination of worms by the end of 21 days when treated with 40–60% of neem seed extract. Weight loss and death were however recorded at 60% concentration of extract raising some concern about the toxicity of the seed extract [38].

2.4 *Carica papaya* Linn. (Caricaceae)

The pawpaw tree is well known for its nutritional and medicinal values. The leaf decoction is used as a galactogogue and in the treatment of tonsillitis, ulcerative stomatitis, hemorrhoids, asthma, urinary tract infections, as poultice for sores and gingivitis and in the treatment of helminth infections. The roots are used as antidote to various poisons. The fruits are used to treat indigestion, chronic diarrhea, ringworm infections, bleeding piles, and amoebic dysentery [39]. Almost all parts of the plant are documented to be used for managing helminth infections. In Ghana, 74% traditional healers used this plant for treating helminth infections [40].

In a comparative assessment of the anthelminthic activity of various parts of the plant, the hydroethanolic extracts of the leaves, stem bark, and seeds of *Carica papaya* were tested against *P. posthuma* as the target organism. The results indicated that all crude extracts prepared were more effective than albendazole in reducing paralysis ($p < 0.0001$) and death times ($p < 0.0001$) of worms. Extracts from the seeds at 2.5 mg/mL were the most effective causing worm paralysis and death at 9.26 ± 0.03 and 20.12 ± 0.01 mins respectively. This was more potent than the standard anthelmintic albendazole at the same concentration which gave paralysis and death times of 19.45 ± 0.57 and 31.43 ± 0.28 mins respectively [41].

2.5 *Combretum mucronatum* Schumach & Thonn. (Combretaceae)

Ethnopharmacological reports from parts of Ghana revealed the extensive use of the leaves of *Combretum mucronatum* for treatment of human and livestock helminth infection [40]. The leaves from this plant species is monographed in the Ghana Herbal Pharmacopeia for the treatment of infections with worms [42].

In a previous study, the alcoholic leaf extract of *C. mucronatum* was assayed *in vitro* for anthelmintic activity against free-living nematode, *Caenorhabditis elegans*

using levamisole as a positive control. The extract demonstrated anthelmintic activity with a worm survival rate of 89.2% at 0.1 mg/mL and 58.1% at 1 mg/mL [40].

In another study, fractions and purified compounds from *C. mucronatum* leaves were tested *in vitro* for their anthelmintic activity against *C. elegans*. Unsubstituted oligomeric proanthocyanidins (PACs) mainly composed of epicatechin units were identified as the active compounds of the hydroethanolic leaf extracts. The compounds demonstrated a dose-dependent anthelmintic activity ranging from 1 to 1000 mM and activity was found to increase with increasing molecular size. The anthelmintic activity was suggested to be by interaction of the PACs with some unidentified proteins of the target organism [43]. Further, the mechanism of anthelmintic activity of the PACs was determined by transcriptome analysis. PACs were found to interact with proteins within the worm's intestinal membrane as well as enzymes and peptides to elicit anthelmintic effects [44]. Another proposed mechanism was interaction of the tannins with cuticular proteins, particularly proline-rich collagen in the worm cuticle [45].

2.6 *Cyperus difformis* Linn. (Cyperaceae)

Cyperus difformis is an annual plant with smooth leaves and fibrous reddish roots. It is native to the subtropical and tropical areas but also distributed and widespread in South Europe, Asia and Americas. It is regarded as one of the world's commonest weeds found growing in wet swampy soils among rice plantation. It is very common in Ghana and traditionally used for the management of scorpion bites and malaria [46].

The anthelmintic and helminth resistance modifying activities of methanol extract of *C. difformis* was investigated against the adult Indian worm, *P. posthuma* using albendazole, mebendazole and levamisole as reference anthelmintics. The extract exhibited a concentration dependent anthelmintic activity against *P. posthuma* with significant ($p < 0.001$) paralysis and death times of 66.67 ± 1.8 and 140.7 ± 2.3 mins respectively at extract concentration of 20 mg/mL [47].

Further the extract at 1, 2 and 5 mg/mL significantly potentiated the activity of albendazole, mebendazole and levamisole against the test organism. In the presence of 2 mg/mL of the extract the paralysis and death times of albendazole (8 mg/mL) against *P. posthuma* were reduced from 41.33 ± 0.33 and 106.67 ± 0.88 min respectively to 33.33 ± 0.88 and 85.67 ± 1.2 min, respectively. Similar results were obtained for mebendazole and levamisole [47].

2.7 *Garcinia cola* Heckel (Guttiferae)

Garcinia cola also known as "bitter cola" is a valuable medicinal plant in African traditional medicine widely accepted for its numerous medicinal properties. It is usually called the wonder plant due to the usefulness of every part of the plant. The seeds are chewed as an aphrodisiac and used to cure cough, dysentery and upper respiratory tract infections [48, 49]. The latex from the stem is used against sexually transmitted infections and applied externally to heal wounds. The sap is used in curing parasitic diseases. Chewing sticks produced from the stems are used as masticatory for nervous alertness and for treating coughs and throat infections [50].

In a previous study, the methanol stem bark extract of *G. cola* (1—50 mg/mL) demonstrated a concentration dependent anthelmintic activity, decreasing paralytic and death times of *P. posthuma* with increasing extract concentrations. At 50 mg/mL, the extract had a paralytic time of 39.29 ± 0.12 min and death time of 54.29 ± 0.01 [51].

2.8 *Morinda lucida* Benth. (Rubiaceae)

Morinda lucida is an evergreen shrub growing from about 3 m to 18 m tall. It has a dense crown with slim, crooked branches. The plant is occasionally grown in home gardens. It is locally called '*konkroma*' in the Ghanaian Akan language. It is a multipurpose species yielding dyes, timber, fuel and traditional medicines. The plant is reported to be used in managing diabetes, hypertension, dysentery, stomach-ache, leprosy and gonorrhea. Traditionally, the stems are used to treat piles while the leaves are used to treat fever. A decoction of the bark or leaf is used in the treatment of jaundice and against itch and ringworm. The leaves and twigs are sold as a medicinal tonic for young children [52].

In a previous study, the methanol stem bark extract of *M. lucida* (10–50 mg/mL) reduced worm motility and caused death of the adult Indian earth worm, *P. posthuma* with a paralytic time of 18.17 ± 0.03 min and death time of 24.34 ± 0.21 min at 50 mg/mL [51].

2.9 *Moringa oleifera* Lam. (Moringaceae)

Moringa oleifera is a fast growing perennial evergreen or deciduous plant which grows up to a maximum height of 7–12 m. It has an open crown of drooping fragile branches bearing feathery foliage of opposite pinnate leaves, a crooked bole and dark gray stem bark. *M. oleifera* has been naturalized in many tropical and subtropical regions of the world including Africa, Arabia, South Asia, South America and India where it is commonly referred to as horseradish tree and drumstick tree [53]. Various parts of the plant are used in traditional medicine to treat various diseases including skin infections, anemia, asthma, bronchitis, catarrh, chest congestion, cholera, diabetes, hypertension and many other illnesses [54].

The foliage of *M. oleifera* was investigated for anthelmintic activity in wild caught *Achatina achatina* Linnaeus (edible snails). After feeding the snails on the foliage for 10 weeks, the proportion of parasitic infection in the treated group was estimated using dissecting and microscopic techniques. At the end of the treatment period, 96% of snails in the untreated group were observed to have their kidneys infected with roundworms as opposed to 24% of snails in the treated group. The percentage prevalence of parasitic infection in the treated and control groups was significantly different ($p < 0.0001$). Similar results were recorded for the infection of the lungs highlighting the anthelmintic value of *M. oleifera* in the control of worm infection in edible snails [55].

2.10 *Ocimum basilicum* Linn (Lamiaceae)

Ocimum basilicum is a tender-growing aromatic annual herb indigenous to West Africa and India. It is commonly called basil or sweet basil and locally known in the Ghanaian Akan language as '*Nunum*'. The herb is ubiquitously known for its therapeutic potentials in African folk medicine. In Ghana, basil is used in its fresh form as spice and flavoring in soups and sauces due to its strong spicy aroma. The whole plant is used to treat worm infestation, inflammation, pain, diarrhea, gastrointestinal infections and eye-related diseases [56].

In vitro anthelmintic activity of the hexane and ethanolic extracts of the fruits of *O. basilicum* was investigated against *Eudrilus eugeniae*. At a concentration range of 0.25–5 mg/mL, the extracts displayed a concentration dependent anthelmintic activity which was observed to be significantly ($p < 0.001$) higher compared to mebendazole-treated worms. At 5 mg/mL, paralysis was observed at 11.85 ± 0.71,

27.90 ± 0.42 and 94.04 ± 2.57 mins for the ethanol extract, hexane extracts and mebendazole-treat worms respectively. Similarly, death of worms was recorded at 24.74 ± 0.42, 85.18 ± 0.07 and 522.77 ± 1.53 mins respectively for the ethanol extract, hexane extracts and mebendazole [57].

2.11 *Paullinia pinnata* L. (Euphorbiaceaae)

Paullinia pinnata is a woody climber growing in tropical regions worldwide. In Ghana, it is locally called '*toantini*' in the Akan language. Preparations from the whole plant is used to treat dysentery. The mashed roots are used as poultice to heal chronic wounds and to treat leprosy. The root decoction is also used to cure coughs, pneumonia, gonorrhea, fractures, bacterial infections and abscesses. It is popularly known for its aphrodisiac property and used to treat erectyle dysfunction [58]. In addition, extracts of leaves and roots have been described for the treatment of helminth infestations particularly ancylostomiasis [40].

The hydroethanolic extract of the roots of *P. pinnata* was investigated in an *in vitro* mortality assay against the free-living nematode *Caenorhabditis elegans* as well as the larval stages of the parasitic helminths: *Ancylostoma caninum*, *Haemonchus contortus*, *Toxocara cati* and *Trichuris vulpis*. From the assay, the extract showed lethal activity against *T. cati* (LC_{50} = 112 μg/mL), *T. vulpis* (LC_{50} = 17 μg/mL), and *C. elegans* (LC_{50} = 2.5 of mg/mL), but not against *A. caninum*. Additionally, the effects of the extract on egg hatching and larval migration of the sheep parasite, *Haemonchus contortus* were investigated *in vitro*, but no inhibitory activity was observed [59].

In another study, the 70% aqueous acetone extract, solvent fractions and isolated compounds from the roots of *P. pinnata* were investigated for anthelmintic against *C. elegans*. From the results, the ethyl acetate fraction showed the highest anthelmintic effects with an LC_{50} of 1.1 mg/mL followed by the crude extract (LC_{50} = 1.9 mg/mL) and the aqueous fraction (LC_{50} = 2.9 mg/mL). Oligomeric proanthocyanidins were identified as the main active compounds. A mortality rate of at least 70% was observed for all proanthocyanidin containing fractions at 1 mg/mL [60].

2.12 *Plumbago zeylanica* Linn. (Plumbaginaceae)

Plumbago zeylanica is a perennial shrub with semi woody stems and numerous branches. It is a valuable medicinal plant widely used in Africa and Asia for the treatments of common ailments like hemorrhoids, diarrhea, leprosy, arthritic pains, toothache and as aphrodisiac and wound healing [61].

In a previous, observations were made for the time taken for different solvent extracts of the leaves of *P. zeylanicum* at concentrations of 300, 100 and 30 mg/mL to paralyze and kill *Pheretima posthuma*. The ethyl acetate extracts showed significant ($p < 0.0001$) concentration-dependent anthelminthic activity with the highest effect at 300 mg/mL causing paralysis at 7.39 ± 0.94 min and death at 11.81 ± 1.10 min. The methanol extract at 300 mg/mL demonstrated slightly lower anthelmintic effect with paralysis at 17.23 ± 1.68 min and death at 21.83 ± 2.60 min [62].

2.13 *Rauwolfia vomitoria* Afzel. (Apocynaceae)

Rauwolfia vomitoria commonly called the African Snakeroot or African Serpent root is a small tree or shrub that grows up to about 20 m tall in tropical Africa. It is locally called '*kakapenpen*' in the Asante dialect of Ghana. In traditional medicine,

the plant is recorded to be used in the treatment of convulsions, malaria fever, insomnia, arthritis, pain, high blood pressure, diabetes, stomach problems and as an emetic. The leaves are applied topically for skin infections, swelling and snake bites. It is placed in the rectum for the expulsion of worms and for dysmenorrhea [46].

The leaves and stem bark of *R. vomitoria* demonstrated significant ($p < 0.001$) anthelmintic activity against the Indian adult earthworm *P. posthuma*. The methanol extracts of the stem bark caused paralysis of worms at 11.17 ± 0.088 min and reduced the death time to 21.67 ± 0.733 similar to the effect of albendazole at 10 mg/mL which had a worm death time of 21.03 ± 0.258 min [63].

2.14 *Sclerocarya birrea* (A. Rich) Hochst (Anacardiaceae)

Sclerocarya birrea is a dioecious small to medium sized tree growing up to about 20 m high and 1.2 m in diameter. The plant is distributed from Gambia, Ghana and Nigeria in West Africa, across Cameroon in Central Africa, to Ethiopia and Sudan in East Africa and to South Africa, usually found growing in open farm lands and natural vegetation [64]. The stem-bark, roots and leaves are used to treat several ailments including diabetes mellitus, diarrhea, dysentery, proctitis, ulcers, inflammation, arthritis, hypertension, skin diseases, and malaria [65].

The anthelmintic activity of the aqueous and ethanolic extracts of the roots of *S. birrea* were evaluated against earth worms. The extracts displayed significant ($p < 0.001$) concentration-dependent anthelmintic activity at 12.00 to 0.1875 mg/mL. The observed effect was higher compared to albendazole-treated worms [66].

2.15 *Vernonia amygdalina* Del. (Asteraceae)

Vernonia amygdalina is tropical shrub which grows up to about 3 m high. The plant is distributed throughout tropical Africa and has been domesticated in some parts of West Africa including Nigeria and Ghana where it is commonly called the bitter leaf. It is a highly valuable vegetable in West and Central Africa which is consumed as part of various dishes. In traditional medicine the leaf decoction is used to treat fever, malaria, diarrhea, dysentery, hepatitis and cough, as a laxative and as a fertility inducer [67]. The root extracts are also used for treating malaria and gastrointestinal disorders. One of the most common medicinal uses of *V. amygdalina* is as a treatment against intestinal worms including nematode infections [68]. The use of the leave decoctions against intestinal worms, especially pinworms was confirmed in an ethnobotanical survey in the Ashanti Region of Ghana [40].

In a previous study, the anthelmintic activity *of V. amygdalina* leaves were investigated against *Lumbricus terrestris* (earth worm). Unlike the negative control groups which remained alive and active after 6 hours of exposure to normal saline, all worms treated with the aqueous and ethanol leaf extracts (50–200 mg/mL) of *V. amygdalina* were noted to be paralyzed within 4.05 ± 1.06 to 59.94 ± 8.25 and 3.56 ± 0.37 to 33.18 ± 12.4 mins respectively ($p < 0.0001$). The effect was concentration dependent [36].

In another study, the stem bark extracts (ethanol and chloroform extracts) of *V. amygdalina* were observed to produce a synergistic anthelmintic effect when combined with the seeds of *Carica papaya* [69].

2.16 *Voacanga Africana* Stapf. (Apocynaceae)

Voacanga africana is a small tree or shrub, reaching up to 6 m tall in height with a low widely spreading crown. In Ghana, it is locally known as '*ofruma*' in the Asante

language. Various plant parts are used medicinally throughout its distribution area [70]. The leaf decoction is used to treat dysentery, diarrhea, cutaneous and subcutaneous parasitic infections, leprosy, oedema, gout, paralysis and convulsion. The stem bark or roots decoctions are used as wound healing agents and used to treat boils, malaria, sexually transmitted diseases like gonorrhea, and skin diseases such as eczema and scabies. They are also taken to treat cardiovascular diseases and rheumatoid arthritis. The leaf latex is put in the teeth to treat dental caries or dripped in the eye to cure ophthalmia [46].

The methanol extracts of the leaves and stem bark *V. africana* were evaluated for *in vitro* anthelmintic activity by determining the effects of the extracts on the paralytic and death time of *P. posthuma* using albendazole as reference. The bark extract (20–50 mg/mL) demonstrated a significant ($p < 0.001$) concentration dependent anthelmintic effect by decreasing the paralysis and death times of worms. At 50 mg/mL, the stem bark extract caused worm paralysis within 7.03 ± 0.491 min and death at 14.77 ± 0.117 min [63].

2.17 *Xylopia aethiopica* (Dunal) A. Rich. (Apocynaceae)

Xylopia aethiopica is popularly known as the African pepper and locally called '*Hwentia*' in the Ghanaian Akan language meaning slender nose, referring to the shape of the fruit. *X. aethiopica* is known for its numerous medicinal properties in African traditional medicine. The bark infusion is used in the treatment of asthma, stomach aches and rheumatism. The bark powder is also applied topically on ulcerous wounds and used locally for the treatment of cancer and stomach ulcers. The root powder is known to relief toothache and pyorrhea [71].

The ethanolic extract of the dried fruits and leaves (300–300 mg/mL) were investigated for anthelmintic activity against earth worms. The anthelmintic activity of the fruit extract was more potent that the leaf extract. Both extracts demonstrated a concentration dependent activity with the fruit extract demonstrating significant paralytic and death times ($p < 0.001$) at 100 and 300 mg/mL [72].

3. Plants with cercaricidal and anti-schistosomal activities identified from Ghana

See **Table 1**.

3.1 *Azadirachta indica* A. Juss (Meliaceae)

[Refer to Section 2.3 for plant description].

The methanol leaf extract of *A. indica* was investigated for cercaricidal activity against freshly shed cercariae of *Schistosoma mansoni*. At a concentration range of 31.2–1000 μg/mL, the leaf extract caused a steady increase in the number of dead cercariae during an observation period of 15 to 180 mins. At 60 mins, 250 μg/mL of extract was found to cause 100% mortality of cercariae. At the end of the observation period (180 mins) the leaf extract recorded an IC_{50} of 27.62 μg/mL which was about four times lower than the effect of the positive control *Balanites aegyptiaca* (IC_{50} of 5.95 μg/mL) [73].

The effect of *A. indica* leaf extract on the viability of adult schistosome worms (i.e. adulticidal effect) was further investigated. At the end of 120 h, the extract at 62.5–1000 μg/mL was found to be lethal to the incopula adult worms. Further in an *in vivo* study, the ability of the leaf extract (500 mg/kg *p.o.*) to reduce the worm recovery and worm burden in *S. mansoni* infected mice was investigated.

Plant	Family	Common name	Part Investigated	Activity Type
Alcornea cordifolia	Euphorbiaceae	Christmas Bush	Leaves	Anthelmintic activity against *Pheretima posthuma* [33]
Alstonia boonei	Apocynaceae	Alstonia	Roots, stem bark	Anthelmintic activity against *Pheretima posthuma, Lubricus terretris* [35, 36]
Azadirachta indica	Meliaceae	Neem	Seeds Leaves	Anthelmintic activity against *Hymenolepsis diminuta*, *Enterbius vermicularis* and hookworm [38] Cercaricidal and adulticidal activity against *Schistosoma mansoni* [73]
Carica papaya	Caricaceae	Pawpaw	Leaves, stem bark, seeds	Anthelmintic activity against *Pheretima posthuma* [41]
Combretum mucronatum	Combretaceae	—	Leaves	Anthelmintic activity against *Caenorhabditis elegans* [40, 43, 45]
Cyperus difformis	Cyperaceae	—	Whole plant	Anthelmintic activity against *Pheretima posthuma* [47]
Dichapetalum crassifolium	Dichapeltaceae	—	Stems, roots	Anti-schistosomal activity against eggs obtained from clinical isolates of *Schistosoma haematobium* [75]
Erythrophloem ivorense	*Euphorbiaceae*	—	Leaves, stem bark Roots	Cercaricidal activity against post-infective larvae (schistosomule) and adult parasite of *Schistosoma mansoni* [77] Cercaricidal activity against freshly shed cercariae from *Schistosoma haematobium* [78]
Garcinia cola	Gutifferae	Bitter kola	Stem bark	Anthelmintic activity against *Pheretima posthuma* [51]
Holarrhena floribunda	Apocynaceae	—	Stem bark	Cercariae from *Schistosoma haematobium*
Morinda lucida	Rubiaceae	—	Stem bark	Anthelmintic activity against *Pheretima posthuma* [51] Cercaricidal activity against *Schistosoma mansoni* cercariae Adulticidal effect against *S. mansoni* adult worms [73]
Moringa oleifera	Moringaceae	Moringa	Foliage	Anthelmintic activity against *round worms in wild edible snails (Achatina achatina)* [55]
Nauclea latifolia	Rubiaceae	African peach	Stem bark	Cercaricidal activity against *Schistosoma mansoni* cercariae Adulticidal effect against *S. mansoni* adult worms [73]
Ocimum basilicum	Lamiaceae	Basil	Fruits	Anthelmintic activity against *Eudrilus eugeniae* [57]

Plant	Family	Common name	Part Investigated	Activity Type
Paullinia pinnata	Euphorbiaceae	—	Roots	Anthelmintic activity against the free-living nematode *Caenorhabditis elegans* and larval stages of the parasitic helminths: *Ancylostoma caninum*, *Haemonchus contortus*, *Toxocara cati* and *Trichuris vulpis* [60]
Plumbago zeylanica	Plumbaginaceae	—	Leaves	Anthelmintic activity against *Pheretima posthuma* [62]
Phyllanthus amarus	Euphorbiaceae	—	Leaves	Cercaricidal activity against *Schistosoma mansoni* cercariae
Rauwolfia vomitoria	Apocynaceae	Snakeroot	Leaves, roots Roots, stem bark	Anthelmintic activity against *Pheretima posthuma* [63] Cercaricidal activity against *Schistosoma mansoni* cercariae Adulticidal effect against *S. mansoni* adult worms [73]
Sclerocarya birrea	Anacardiaceae		Roots	Anthelmintic activity against *Lumbricus terrestris* [66]
Vernonia amygdalina	Asteraceae	Bitter leaf	Leaves, stem bark Leaves	Anthelmintic activity against *Lumbricus terrestris* [36] Cercaricidal activity against *Schistosoma mansoni* cercariae Adulticidal effect against *S. mansoni* adult worms [73]
Voacanga africana	Apocynaceae	—	Leaf, stem bark	Anthelmintic activity against *Pheretima posthuma* [63]
Xylopia aethiopica	Apocynaceae	African black pepper	Fruits, leaves	Anthelmintic activity against *Lumbricus terrestris* [72]

Table 1.
Medicinal plants from Ghana with anthelmintic and anti-schistosomal activity.

After a two-week period of treatment, the mean number of worms recovered from *A. indica*-treated mice was 19.80 ± 8.194 which was significantly lesser than that of the untreated mice (40.20 ± 3.072) [73].

The effect of the extract on the weight of spleen and liver of infected mice were all significantly lesser in the *A. indica*-treated group than that of the untreated group ($p < 0.05$). Organ histology also revealed only few granulomas which were smaller in diameter in the treatment groups whereas those in the untreated were severe ($p < 0.05$). Treated cercariae-infected mice group also had relatively less severe inflammatory cell infiltration compared with untreated group [73].

3.2 *Dichapetalum crassifolium* Chodat (Dichapetalaceae)

Dichapetalum crassifolium is a scandent shrub, about 1.5 m tall usually found growing in the rain forest, shady places, primitive woods and rocky areas of African countries including Ghana, Angola, Benin, Cameroon, Ivory Coast, Liberia, Nigeria, Sierra Leone, Tanzania, Togo and Zambia [74].

Crude extracts (pet-ether, ethyl acetate and methanol) and isolated triterpenoids from the stems and roots of *D. crassifolium* were investigated for anti-schistosomal activity against eggs obtained from clinical isolates of *Schistosoma haematobium* using the 96-well plate-egg hatch assay [75].

For the stem extracts, the ovicidal potency was in the following order petroleum ether (IC_{50} = 443.70) > EtOAc (IC_{50} = 638.00) > MeOH (IC_{50} = 893.70 μg/mL). The IC_{50} values for the root extracts were 248.60, 546.40, and 566.30 μg/mL respectively for the EtOAc, pet-ether and MeOH extracts.

The isolated compounds (Friedelan-3-one, β-Sitosterol/stigmasterol, Dichapetalin M and Dichapetalin A) showed higher ovicidal activity than the extracts though activities for both extracts and compounds were lower compared to the standard drug, praziquantel. The highest ovicidal potency was exhibited by β-sitosterol/stigmasterol mixture with an IC_{50} of 177.90 μg/mL which was about 11 times less potent than praziquantel (15.47 ± 0.06 μg/mL). The next highest was dichapetalin A (151.10 μg/mL) whiles friedelan-3-one showed the least potency with IC_{50} of 378.10 μg/mL. From the root extract, Dichapetalin M showed ovicidal effect with IC_{50} of 191.00 μg/mL [75].

3.3 *Erythrophleum ivorense* Afzel (Euphorbiaceae)

E. ivorense is a large tree which grows to about 40 m tall, with a cylindrical bole, sometimes fluted at the base. It is widely distributed in the evergreen primary and secondary forests of tropical Africa where it is commonly called by names like 'forest ordeal tree', 'red water tree' and 'sasswood tree'. Among the Akan tribe in Ghana, it is known as '*potrodum*'. The stem-bark and roots are usually employed in the treatment of epilepsy, emesis, pain, oedema, constipation and worm infestations [76].

The cercaricidal activity of the leaf and stem bark extracts of *E. ivorense* was investigated against two developmental stages of *Schistosoma mansoni* namely: the post-infective larvae (schistosomule) and the adult parasite. Various solvent fractions were assayed against the schitosomules at a concentration range of 0.31–100 μg/mL and against adult parasites at 1.25 mg/mL. The acetone fractions of both leaf and bark demonstrated the highest anti-schistosomal activity causing severe phenotypic alterations (immobility/inactivity, change in shape, translucence, surface disintegration) and death of schistosomules at all dilutions (except 0.31 μg/mL) at 24 h and 48 h. For adult parasites, severe phenotypic changes specifically damage to the adult parasite's tegument (surface) was observed for the acetone fraction of

the stem bark extract. The adult worms were observed to be uncoordinated by 5 h, darkened in color by 24 h and died at 48 h exhibiting tegumental damage [77].

In another study, the *in vitro* cercaricidal activity of solvent fractions and isolated compounds from the root bark of *E. ivorense* was investigated against freshly shed cercariae from *Schistosoma haematobium*. Whereas the cercariae showed normal viability without any morphological changes (tail loss) throughout the entire duration of the experiment in the untreated group, exposure of cercariae to the crude hydro-ethanolic extract, its fractions and compounds caused a concentration and time-dependent decrease in viability of cercariae. Within two hours of incubation, all cercariae died at the various concentrations of test compounds and extracts. Eriodictyol, was the most potent compound with an IC_{50} of 1.23 ± 0.05 μg/mL. All test samples exhibited a much higher cercaricidal activity than the standard drug praziquantel which caused only 40% mortality of cercariae at the highest concentration tested (IC_{50} = 695.50 ± 0.05 μg/mL) [78].

3.4 *Holarrhena floribunda* (G. Don) Dur. & Schinz. (Apocynaceae)

Holarrhena floribunda is native to West Africa and is known in Ghana as '*osese*' among the Akans. The plant is traditionally used in the treatment of malaria, fever and bareness in females. It has antifungal, antibacterial and antidiabetic properties [79, 80].

The hydroethanolic and alkaloidal extracts from the stem bark of *H. floribunda* were tested on cercariae from *Schistosoma haematobium* at concentrations between 15.625 and 500.00 μg/mL. After 180 mins of contact with test samples, the ethanolic extract exhibited the highest cercaricidal potency with an IC_{50} of 20.09 ± 1.11 μg/mL higher than the effect of paraziquantel (IC_{50} = 695.50 ± 1.12). The alkaloidal extract also exhibited cercaricidal potency with an IC_{50} of 53.20 ± 1.33 μg/mL. The isolated compounds: holonamine, holadienine and conessine exhibited cercaricidal potency with IC_{50} values of 53.24 ± 1.28, 470.80 ± 1.00 and 33.28 ± 1.04 respectively. The results confirmed the activity of *Holarrhena floribunda* against *S. heamatobium* ceracriae [81].

3.5 *Morinda lucida* Benth (Rubiaceae)

[Refer to Section 2.8 for plant description].

In a previous study, the cercaricidal activity of the methanol stem bark extract of *M. lucida* was carried out. The extract at a concentration of 500 μg/mL elicited 100% mortality of *S. mansoni* cercariae within 120 mins of exposure giving an IC_{50} value of 262.3 μg/mL, which was however lower than the effect of the positive control *Balanites aegyptiaca* (IC50 of 5.95 μg/mL). Further, the *in vitro* adulticidal effect of the stem bark extract on adult schistosome worms revealed that at a concentration of 125–1000 μg/mL, the extract was found to be lethal to the adult worms within 120 h of exposure [73].

3.6 *Nauclea latifolia* Carl Lin. (Rubiaceae)

Nauclea latifolia, commonly called the African peach, is a deciduous shrub with an open canopy distributed throughout tropical and savanna regions of Africa and Asia. It varies widely in height from around 10–30 m according to soil and moisture conditions. The plant is used against various medical conditions such as diabetes, fever, indigestion and cough [82].

Previous studies on the cercaricidal activity the methanolic extract of stem bark of *N. latifolia* revealed 100% mortality of *S. mansoni* cercariae at a concentration

of 250 μg/mL at 120 min (IC_{50} = 195.9 μg/mL). Further the extract was found to exhibit schistomicidal effect being lethal to the adult incopula worms at a concentration range of 500–1000 μg/mL within 120 mins of exposure [73].

3.7 *Phyllanthus amarus* Schum. and Thonn. (Euphorbiaceae)

P. amarus is a small herb bearing ascending herbaceous branches normally found around coastal and muddy areas. The whole plant is used in the treatment of gonorrhea, menorrhagia and other urinary and sexually transmitted infections. It is useful in gastropathy, diarrhea, dysentery, intermittent fevers, ophthalmopathy, scabies, ulcers and wounds [83].

The methanolic extract (250 μg/mL) of *P. amarus* leaves exhibited moderate cercaricidal activity on freshly shed *S. mansoni* cercariae causing 100% mortality of cercariae within 180 mins of exposure (IC_{50} = 250.4 μg/mL). It was further established that at 125–1000 μg/mL, the extract caused a drastic reduction in the viability of adult worms [73].

3.8 *Rauwolfia vomitoria* Afzel. (Apocynaceae)

[Refer to Section 2.13 for plant description].

The root and stem bark of *Rauwolfia vomitoria* were evaluated for schistosomicidal effect on two different parasitic stages of *Schistosoma mansoni* i.e. cercariae and adult worms [84].

The ethanolic extract of the root and stem bark were both found to be active against the cercariae and adult worms. At a concentration range of 62.5–1000 μg/mL the stem bark extract exhibited significant anti-cercarial activity ($p < 0.05$) with an LC_{50} of 207.4 and 61.18 μg/mL after 1 and 2 h of exposure respectively. At the highest concentration (1000 μg/mL), there was 100% mortality of cercariae within 90 min of exposure. The roots were less active than the stem bark showing activity at a higher concentration range of 250–1000 μg/mL. The schistomicidal activity of the stem bark and roots were further determined against adult worms. All adult worms exposed to the concentrations range of 250–1000 μg/mL for both plant parts died within 120 h of incubation [84].

3.9 *Vernonia amygdalina* Del. (Asteraceae)

[Refer to Section 2.15 for plant description].

In a previous study, the evaluation of the cercaricidal and schistosomicidal activities of the methanol extract of the leaves of *V. amygdalina* revealed significant potency response. At 250 μg/mL, the extract exhibited cercaricidal activity with an IC_{50} of 35.84 μg/mL within 180 min of exposure. Further, the extract was found to reduce the viability of adult schistosome worms *in vitro* at 250–1000 μg/mL.

The ability of the leaf extract (500 mg/kg *p.o.*) to reduce the worm recovery and worm burden in *S. mansoni* infected mice was further investigated in an *in vivo* study. After a two-week period of treatment, the mean number of worms recovered from *V. amygdalina*-treated mice was 12.00 ± 1.549, indicating 48.9%, worm burden which was significantly lower than that of the untreated group (40.20 ± 3.072). While there was significant increase in the weight of the liver and spleen of the untreated infected mice with marked formation of granuloma, *V. amygdalina*-treat infected mice showed no increase in liver or spleen size and had few granulomas which were smaller in diameter with relatively less severe inflammatory cell infiltration compared [73].

4. Conclusion

The anthelmintic and anti-schistosomal activities of some medicinal plants employed in Ghanaian traditional medicine have been validated. For most of these plants however, the specific bioactive constituents are not yet identified. It is therefore imperative that further studies to isolate and verify the constituents responsible for the observed activities be performed. Further, the evaluation of safety profiles will add substantial value to the reported bioactivities and make these plants attractive for adaptation to pharmaceutical companies for further development.

Conflict of interest

Authors have no conflict of interest to declare.

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