Medicinal Plants as Promising Alternatives for Treating Helminthiasis: A review

Douti Fekandine Victoire[1]*, Djeri Bouraima[1] and Karou Damitoti Simplice[1]

[1]École Supérieure des Techniques Biologiques et Alimentaires (ESTBA), Université de Lomé, Lomé, Togo.

Abstract

Introduction: Helminth infections pose a significant threat to public health and affect both humans and animals. These infections affect nearly one-fifth of the global population and result in substantial livestock losses. These infections are treated with anthelmintic drugs, but the parasites' resistance to these common drugs suggests the need for new anthelminthic agents. This review elucidates the effectiveness of vegetable compounds against helminth infections with a mode of action similar to that of conventional anthelminthics.

Methods: Although several hundred articles were identified, this review found over one hundred and thirty articles relevant to our keywords after sorting them. These articles were selected from databases such as Google Scholar, PubMed, ScienceDirect, and BMC, using search terms such as "helminths," "anthelmintic plants," and "alternative medicine." The selected studies focused on helminthiasis and the anthelmintic activity of plants. WHO data were also used to obtain information on the prevalence and epidemiology of helminthiasis.

Results: Most conventional anthelminthics, commonly used to treat helminths, belong to the benzimidazole (albendazole, mebendazole), macrocyclic lactone (ivermectin), and pyrazinoisoquinolines (praziquantel) families. However, their frequent use has led to resistance, as reported in numerous studies.

Nevertheless, plants can be an alternative, as many plants are used in traditional medicine to treat helminth infections. The anthelmintic effects of these plants are often attributed to their secondary metabolites, including tannins, polyphenols, flavonoids, alkaloids, saponins, steroids, terpenoids, essential oils, and fatty acids. These compounds act by inhibiting larval development, egg hatching, and worm motility by damaging worm cuticles, which leads to parasite paralysis and death. However, researchers must focus on clinical tests after isolating the bioactive compound of these plants in the view to setup new anthelmintic drugs to face resistances observed.

Conclusion: Many medicinal plants contain anthelmintic molecules that can be used as alternative treatments for helminths. Thus, researchers must investigate more on clinical tests of the isolated bioactive compounds for setting up new anthelminthic drugs.

Keywords: Helminth infections, anthelmintic drugs, resistance, plants, alternative medicine.

Introduction

Helminthiasis refers to infections caused by parasitic worms, called helminths, in their larval or adult stages. These parasites are classified into three main groups on the basis of their morphology: nematodes (roundworms), cestodes (segmented flatworms), and trematodes (non-segmented flatworms) (1). Nematodes include intestinal worms and filarial worms, which cause lymphatic filariasis and onchocerciasis, respectively. Cestodes are flatworms that cause taeniasis, while trematodes are flukes that cause fluke disease (1). These multicellular organisms feed on the host's nutrients once inside the body, causing diseases in organs such as the gastrointestinal tract, tissues, and lymphatic system (2).

Helminth infections are a significant public health concern for both humans and animals. They infect nearly one-fifth of the world's population and cause substantial losses of

livestock (3). Most helminth infections are classified as neglected tropical diseases (NTDs) (4) due to the lack of funding for drug discovery (5, 6). More than two billion people are estimated to be affected worldwide (7, 8), particularly in tropical and subtropical regions where sanitary conditions are poor (9). The highest prevalence is found in sub-Saharan Africa, Asia, and South America (10, 11). An estimated 500 million people in sub-Saharan Africa are affected (12) with notable concentrations of cases of soil-transmitted helminthiasis (STH), schistosomiasis, lymphatic filariasis, and other diseases (10). These endemic areas are characterized by inadequate sanitation and limited access to clean drinking water (2).

Togo has made significant efforts to combat these diseases. In 2017, it became the first sub-Saharan African country to eliminate lymphatic filariasis as a public health problem (13). However, despite these advances, STH remains endemic in six rural villages in central Togo, affecting 74.38% of the population (14). This persistence is due to conditions that favor transmission, such as limited access to safe drinking water and adequate sanitation facilities. Symptoms of helminthiasis depend on several factors, including the species of helminth, the severity of the infection, and the age of the host. Common symptoms include anemia, eosinophilia, liver and spleen inflammation, malnutrition, intestinal obstruction, weight loss, and pneumonia (15).

Treatment of helminthiasis mainly involves administering anthelmintic drugs (16). While these drugs are effective, their extensive use has resulted in resistance among certain parasite species (17). Additionally, these treatments can cause undesirable side effects, including gastrointestinal disorders, allergic reactions, and, in rare cases, neurotoxic effects (18). Furthermore, access to these drugs is limited in many rural areas of sub-Saharan Africa because of cost, distribution logistics, and lack of awareness among affected populations. Unmet therapeutic needs lead to high mortality and disability rates, creating a significant social and economic burden (19). These challenges underscore the urgent need for more accessible, effective, and sustainable therapeutic alternatives (20). Drug innovation outcomes for a particular disease reflect investment in research and development (R&D). However, it is known that drug discovery and development (DDD) is costly and inherently risky. Therefore, funding limitations and the insufficient economic returns of NTD drugs restrict innovation efforts in this area (21).

For centuries, medicinal plants have been used in traditional medicine to treat various conditions, including parasitic infections. These plants are rich sources of bioactive compounds with potential anthelmintic properties. Recent studies have demonstrated the effectiveness of certain plant extracts against particular helminths, indicating their potential as alternatives to synthetic drugs (7). The use of medicinal plants has several advantages. They are generally more accessible and affordable for local populations, highly culturally acceptable, and offer a variety of mechanisms of action, thereby reducing the risk of resistance development (20). Additionally, scientific exploration of these plants can lead to the discovery of new therapeutic compounds and promote traditional knowledge (22).

The purpose of this review is to identify and analyze medicinal plants with demonstrated anthelmintic activity, particularly those used in sub-Saharan Africa. This review examines the available scientific evidence regarding plant efficacy, mechanisms of action, safety, and potential integration into strategies to control helminthiasis. The goal is to encourage the use of medicinal plants as alternative treatments for helminths and to create a comprehensive database of plants used to treat helminthiasis to guide future research on anthelmintic agents.

Methods

Several hundred articles were identified in total, but after careful screening, 137 were selected. Our selection criteria were articles whose studies focused on helminthiasis and the anthelmintic activity of plants. After evaluating the methods used and the results obtained, we only included the most relevant articles. We found publications by searching online article databases, such as: Google Scholar, PubMed, ScienceDirect and BMC. The World Health Organization website was used to identify the prevalence and epidemiology of helminthiasis (Figure 1). All of the consulted articles were written in English. The search terms "helminths" and "anthelmintic plants" were used in conjunction with "alternative medicine" to identify relevant articles.

Results and discussion
Epidemiology and significance of helminth infections

Since the beginning of human history, helminths have infested humans and they still do today. Somes studies reveal that infections caused by human intestinal parasites date back to prehistoric times (23, 24). Studies estimate that hundreds of millions of people worldwide are infected with helminths (25). These parasitic worm infections evolve over time in humans (26). Helminth infections pose a serious threat to public health in developing countries (27). The epidemiology of helminth infections is influenced by several factors, including population growth, standard of living, global warming (28), age, and geographical variations (29, 30). Hookworm infection affects nearly 40 to 50 million school-age children and 7 million pregnant women, for whom it is a leading cause of anemia.
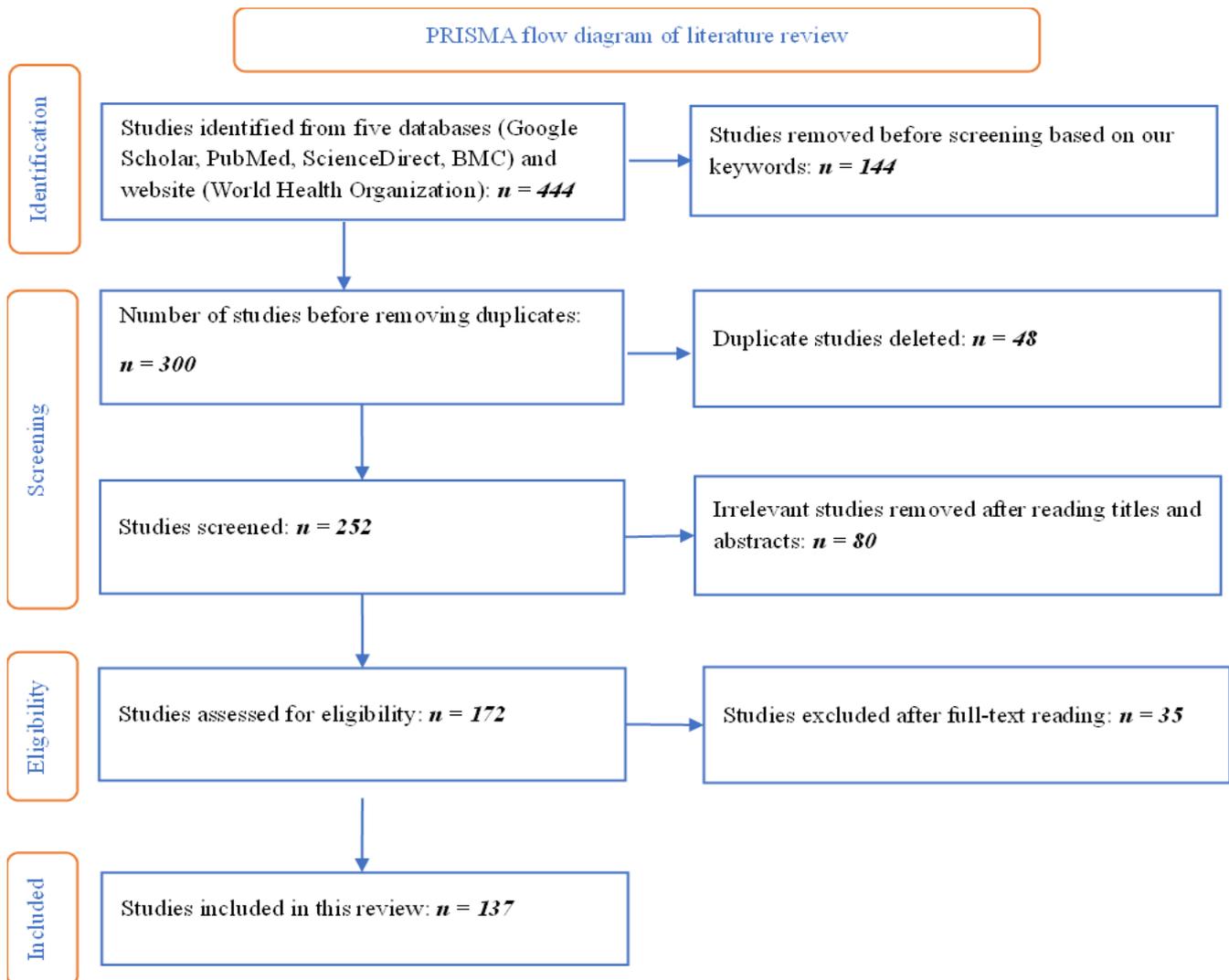
Figure 1: *Representation of literature review steps. A total of 444 articles were identified and selected on Google Scholar, PubMed, ScienceDirect, BMC and World Health Organization. After eligibility test, 172 were used for this based on their relevance to the topic. Finally, 137 were include in this review*

Lymphatic filariasis affects 46 to 51 million people, and onchocerciasis affects nearly 37 million people (12). Hyperreactive onchocerciasis is characterized by an excessive immune response involving an increase in pro-inflammatory Th17 and Th2 cells. This response is accompanied by a reduction in regulatory T cells, which typically moderate immune responses (31). Helminthiasis prevalence in the adult population increased despite the implementation of the Mass Drug Administration (MDA) in school-aged children (32). The morbidity associated with helminthiasis considerably affects children's cognitive development and physical growth (8, 9, 27) ; representing a significant medical and economic burden .

Consequently, morbidity and mortality rates associated with helminths are increasing worldwide (8). Some of these infections are classified as neglected tropical diseases (NTDs) (10), as they primarily affect impoverished communities (33). The World Health Organization (WHO) has identified seventeen NTDs (34). However, the WHO's MDA programs, which aim to reduce or eliminate these diseases, currently target seven of them: lymphatic filariasis, onchocerciasis, schistosomiasis, blinding trachoma, and geohelminthiasis (ascariasis, trichuriasis, and hookworm) (35). Taeniasis/cysticercosis is one of the seventeen NTDs (36). It is an infection that affects humans and animals, including cattle and pigs, and is caused by Taenia saginata or Taenia solium. These two species are prevalent in several regions of the world, including Africa. Cases have been reported in the Middle East and North Africa (37), Taeniasis/cysticercosis is one of the seventeen NTDs (36).

It is an infection that affects humans and animals, including cattle and pigs, and is caused by Taenia saginata or Taenia solium. These two species are prevalent in several regions of the world, including Africa. Cases have been reported in the Middle East and North Africa (37), East and South Africa (38, 39) and Central and West Africa, where they cause significant economic losses (40). A dose of praziquantel 10 mg/kg, niclosamide 2 g, or albendazole 400 mg in triple doses could be used in MDA programs to combat Taenia solium cysticercosis (41). However, a recent study investigated the effectiveness of a single dose of niclosamide, which is only 75% effective (42). Therefore, there is an urgent need to develop new therapeutic solutions, as existing treatments for helminth infections are limited.

Mechanism of action and limitations of some commonly used anthelmintics

There are only a few drugs currently available to treat these infections. Albendazole, oxamniquine, praziquantel, and ivermectin are the most common ones used to treat human helminthiasis (27). These anthelmintics primarily target structures or functions essential to the survival of helminths.

Albendazole, a benzimidazole derivative, binds to the parasite's β-tubulins, thereby inhibiting their polymerization into microtubules (43). This disruption interferes with several processes vital to parasite survival, including intracellular transport, glucose uptake, cell division, and cytoskeletal structure, ultimately leading to its immobilization and death (44).

On the other hand, ivermectin acts on glutamate-dependent chloride channels (GluCls), which are present in the muscle and nerve cells of nematodes (43). GluCls are found in invertebrates, but not in humans (7). Binding to these channels induces hyperpolarization through the influx of chloride ions, which leads to the death of the worm (5). Additionally, GluCls exhibit high affinity for ivermectin, correlating with this drug's anthelmintic potency (28). Ivermectin acts as an antagonist of gamma-aminobutyric acid (GABA) and nicotinic receptors on parasite muscle cells (45). This results in the inhibition of movement and feeding, which leads to nematode death. However, ivermectin is microfilaricidal and does not effectively kill adult worms; it only blocks the release of microfilariae for a few months after treatment (15).

Oxamniquine, which is primarily used to treat Schistosoma mansoni infections (46), is a prodrug activated by the parasite-specific enzyme sulfotransferase (SmSULT) (47). The resulting reactive metabolite covalently binds to DNA, causing irreversible alterations in cellular functions, particularly in male Schistosoma mansoni worms (48).

On the other hand, praziquantel acts by increasing the parasite's membrane permeability to calcium (Ca^{2+}). This causes muscle contraction, leading to intense muscle paralysis and disintegration of the integument. Thus, the parasite is exposed to the host's immune responses, particularly inflammatory reactions (49, 50). Praziquantel is much more active than oxamniquine because it is effective against all species of adult schistosomes. However, it remains ineffective against their immature forms for reasons that are still unknown (51). Praziquantel is also effective against other species of trematodes and acts against the larval, immature, and mature stages of cestodes. It is particularly effective in treating taeniasis and cysticercosis (52).

Unfortunately, the use of the same drugs for such a long time has led to the emergence of resistance. Several studies have reported the reduced efficacy of currently available human anthelmintics, and the scope of resistance is likely to increase (53). Additionally, resistance to an anthelmintic in a given class tends to be accompanied by resistance to other anthelmintics in the same class, a phenomenon known as secondary resistance. This occurs because anthelmintics in the same class act similarly (43). Thus, new innovative therapies with different modes of action for sustainable anthelmintic control are needed (54).

Knowing the mechanism of action of anthelminthics helps us understand their resistance process and how to address it.

Problems related to anthelmintic resistance

The previously described mechanisms of action are fundamental to the effectiveness of antiparasitic treatments and the prevention of resistance. However, cases of resistance to anthelmintics in certain parasites have been reported in recent years (55) and pose a significant threat to human and animal health (28). In vivo methods, such as the stool egg count reduction test, and in vitro methods, such as egg hatching tests, larval motility tests, larval development tests, and PCR, can detect anthelmintic resistance (17).

This is exemplified by a study conducted by Jacob et al. who reported that the emergence of albendazole resistance is associated with the E198K mutation in the parasite's β-tubulin gene (44). This mutation replaces glutamic acid (E) at position 198 with lysine (K), thereby altering albendazole's binding affinity. Glutamic acid is negatively charged, while lysine is positively charged. This change disrupts essential electrostatic interactions, reducing albendazole's ability to properly bind to the β-tubulin protein (5).

Ivermectin resistance was also indicated. UNC-9 is a gap junction protein that facilitates electrical communication between neurons and plays a pivotal role in neuronal signaling and locomotion in Caenorhabditis elegans. In

UNC-9 mutants, impaired electrical coupling between motor neurons alters how signals propagate, which can make ivermectin less effective. This is because the coordinated hyperactivation that normally causes paralysis is blunted. Thus, the mutation limits ivermectin's ability to induce neuromuscular failure and provides the UNC-9 mutant worms with a survival advantage (5).

Chevalier et al. (2019) demonstrated that resistance to oxamniquine is due to recessive, loss-of-function mutations in the sulfotransferase (SmSULT-OR) of the parasitic organism Schistosoma mansoni, as well as several other mutations (p.W120R, p.N171IfsX28), including a confirmed deletion (p.E142del). These mutations are widespread in natural parasite populations under minimal drug pressure and predate the deployment of oxamniquine (56).

Reduced sensitivity to praziquantel has also been detected in parasites from patients who have failed treatment with praziquantel. Da Silva et al. reported resistance to praziquantel in Senegal. The administration of a 40 mg/kg dose of praziquantel during a schistosomiasis epidemic resulted in cure rates of only 18%-39% (50).
In response to cases of resistance to pharmaceutical drugs, studies are being conducted to develop new, sustainable, effective, innovative, and safe therapeutic solutions based on natural plant products (57).

Potential of medicinal plants as an alternative

Medicinal plants play an important role in managing parasitic diseases in humans and livestock, particularly in Africa (58). Humans have used them to treat ailments since several centuries, and they are still used daily around the world to treat various illnesses (59). Their accessibility and low cost mean that the global population is increasingly turning to them (60). Currently, approximately 80% of the global population uses plants directly or indirectly to treat diseases (61). Approximately 20,000 plant species are estimated to be used in traditional medicine worldwide, demonstrating the potential of natural products and the possibility of developing new essential antiparasitic drugs from these plants (62). However, of the 71 new drugs approved between 1981 and 2019, only 7 were derived entirely from natural products. Unfortunately, there are currently no anthelmintic drugs approved for use that have been developed from plant sources (58).

In Africa, most of the population relies on traditional, plant-based medicine for their primary health needs (63, 64). Certain plants have been identified as treatments for helminthiasis in regions where it is prevalent (65). For example, in southern Africa, the use of Zanthoxylum capense (Thumb.) Harv., Acacia karroo Hayne, and Abrus precatorius (L.) to treat helminth infections, schistosomiasis, leishmaniasis, and trypanosomiasis has been reported by Cock et al. (66). In Central Africa, specifically in Gabon, a survey listed 24 plants used to treat intestinal, cutaneous, and ocular helminthiasis. The most commonly cited plants are Cylicodiscus gabonensis Harms, Zanthoxylum gilletii (De Wild.), Plagiostyles Africana (Müll.Arg.), Duguetia barteri (Benth.) Chatrou, and Annickia chlorantha (Oliv.) Setten & Maas (67). Another study in northern Cameroon listed 22 anthelmintic plants used in traditional medicine. Tephrosia pedicellata Baker, Aristolochia baetica (L.), and Abelmochus esculentus (Okra) were the most effective (100%) against the gastrointestinal nematode Haemonchus contortus (68). In East Africa, particularly in Kenya, medicinal plants are the primary treatment for helminthiasis in human and veterinary medicine (69).

Several medicinal plants in sub-Saharan Africa are known for their ability to treat parasitic diseases, including leishmaniasis, trypanosomiasis, helminthic infections, onchocerciasis, lymphatic filariasis, schistosomiasis, toxoplasmosis, and echinococcosis (70). However, more research is needed to evaluate the efficacy and safety of these plants in order to develop accessible, affordable, and safe herbal therapies (71).

In vitro anthelminthic activities

An *in vitro* study demonstrated that three plants known for their anthelmintic properties — Aframomum melegueta K. Schum., Xylopia aethiopica (Dunal) A. Rich., and Khaya senegalensis A. Juss. — possessed anti-inflammatory and anti-Th17-Th2 activity in subjects with hyperreactive onchocerciasis (72). A study made by Waterman et al. revealed strong in vitro anthelmintic activity in eight of the seventeen plant species tested on the levamisole-resistant strain of Caenorhabditis elegans. These include Acacia polyacantha Willd., Anogeissus leiocarpus (DC.) Guill. & Perr., Bridelia micrantha (Hochst.) Baill, Cassia sieberiana DC., Combretum nigricans Lepr. ex Guill. & Perr., Grewia bicolor Juss., Strychnos spinosa Lam., and Ziziphus mucronata Willd. (73). Another study examining 29 medicinal plants used in Ghana revealed that Clausena anisata Willd., Zanthoxylum zanthoxyloides Lam., and Punica granatum (L.), exhibited stronger in vitro anthelmintic activity against Ascaris suum (74). A survey conducted by Ataba et al. in Togo reported that Aframomum melegueta K. Schum., Khaya senegalensis A. Juss., and Xylopia aethiopica (Dunal) A. Rich., were the three most widely used of the 41 cited plants and possessed anthelmintic properties against Litomosoides sigmodontis microfilariae (75). Thus, Douti et al. demonstrated the in vitro anthelmintic activity of hydroethanolic extracts and fractions (dichloromethane, ether, and aqueous) of Aframomum melegueta and Xylopia aethiopica , on adult worms and Tænia spp cells (76).

In vivo anthelminthic activities

In vivo studies are the most useful method for validating the anthelmintic potential of plants (77). However, most studies that screen for anthelmintic activity in plant extracts are performed in vitro rather than in vivo (78). Ali et al. reported that that in vitro studies were almost five times greater than in vivo studies, and they also highlighted inconsistent toxicology assessments across studies (79). In practice, many anthelmintic studies either omit or limit rigorous toxicity testing to a single cytotoxicity assay, so host toxicity issues remain under-evaluated (80). For example, Xylopia aethiopica (Dunal) A. Rich., known for its anthelmintic properties, was found to be not cytotoxic in cytotoxicity testing, but toxicological impact assessment revealed inflammation and vascular congestion of the liver and kidneys (81, 82).

Hu *et al.* also reported a lack of studies on the optimization of the clinical efficacy of potential anthelmintic treatments (83). Thus, numerous plant extracts showing in vitro or in vivo efficacy have not progressed to the clinical validation of new anthelmintics. According to Nixon et al., most promising preclinical hits rarely become clinically validated drugs due to barriers in bringing anthelmintics to human clinical trials (84). A review compiling plant-derived leads repeatedly emphasizes that, although many extracts show *in vitro* or *in vivo* efficacy, clinical evaluation in humans is lacking (58).

However, all of these tests are necessary to confirm the efficacy and safety of plant-based drugs for pharmacological validation before new anthelmintics can be developed.

Main plant metabolites with anthelmintic activity

Authors In recent decades, researchers have focused on developing medicines from plant extracts because their success rate is higher than that of chemical synthesis (85). Plants are a source of several broad-spectrum secondary metabolites that contribute to their defense mechanisms (28) and can serve as a natural solution for parasite resistance. These metabolites can be classified into several categories. For example, alkaloids are known for their analgesic properties, phenolic compounds can act as antioxidants, flavonoids have anti-inflammatory properties, and saponins can act as diuretics. Tannins act as natural antibiotics (59). Plants also contain fatty acids that paralyze or even kill parasitic worms (86) ; and essential oils that prevent egg hatching and larval and adult developmen (87). A study by Mondal et al. showed that the anthelmintic activity of the ethanolic extract of Alternanthera sessilis (L.), against Haemonchus contortus is due to phytochemical compounds,

including flavonoids, saponins, steroids, tannins, terpenoids, and reducing sugars (88). Additionally, polyphenolic compounds, particularly coumarin and caffeic acid, have been reported to have anthelmintic activity against Cooperia punctata, a nematode found in cattle (89). Polyphenols are widely used in traditional medicine to treat nematode infections (90). A study by Jato et al. revealed that polyphenols and terpenoids are the most frequently cited anthelmintic compounds (58). The anthelmintic activity of condensed tannins has also been documented. They bind to cuticle proteins, causing the cuticle to break down. They also inhibit energy production by the worm, leading to its death by energy depletion (91). A study by Ndjonka et al. on medicinal plants and their natural compounds revealed that tannins, alkaloids, triterpenoids, and essential oils were active against Onchocerca spp (92). Maestrini et al. demonstrated that saponins from Medicago polymorpha (L.), cultivars exhibited significant anthelmintic activity by inhibiting the hatching of gastrointestinal strongyle nematode eggs in sheep (93).

The anthelmintic activities of these secondary metabolites are due to their bioactive compounds. Consequently, research is increasingly focused on identifying and isolating these molecules because this is the first step in developing new anthelmintic drugs.

Bioactive compounds isolated from plants with anthelmintic activity

In general, the medicinal properties of plants are due to the bioactive compounds they contain (7). Certain active compounds isolated from plants have demonstrated anthelmintic activity against different helminth species. For example, luteolin, a compound derived from Ajania nubigena (Wallich ex Candolle), has demonstrated broad-spectrum activity against Schistosoma mansoni and Trichuris muris. It has also been shown to be effective against schistosome larvae, which are naturally resistant to praziquantel, the standard treatment (94). Additionally, quercetin, a naturally occurring plant flavonoid, caused lesions in the Haemonchus contortus parasite, demonstrating the anthelmintic activity of this compound against all stages of worm development (95).

As a mode of action, the bioactive molecules and phytochemical compounds in medicinal plants can act individually or synergistically against parasites (59). Some act as acetylcholinesterase inhibitors, which leads to an accumulation of acetylcholine and causes flaccid paralysis in worms. Momordica charantia (L.), for example, is a plant rich in phytochemical compounds, including the alkaloid charantin and the saponins karavilagenin, karaviloside, kuguacine, momordicine, momordicoside, and momordinate, all of which have antiparasitic properties (96). Other anthelmintics cause paralysis in worms by inducing oxidative

stress and altering the activity of stress response enzymes, such as catalase, superoxide dismutase, and glutathione Peroxidase. This occurs with certain flavonoids, including quercetin (95).

Fahs and colleagues demonstrated that a group of avocado fatty alcohols/acetates (AFAs) exhibited anthelmintic activity by interfering with the lipid metabolism of the nematodes used in the study (3). This mode of action involves impaired respiration due to mitochondrial damage, which causes paralysis of the worms. Biochemical and genetic tests revealed that AFAs inhibit POD-2, the gene that encodes acetyl-CoA carboxylase, an enzyme that limits lipid biosynthesis (3).

These studies demonstrate that, in many cases, these compounds impact helminth survival and can therefore be exploited by the pharmaceutical industry or medicine.

Table 1 lists anthelmintic plants with identified bioactive compounds, their metabolite categories, target helminths, and mechanisms of action.

Methodologies used to assess the anthelmintic activity of plants

Although there are many challenges associated with the use of natural products, such as extraction difficulties and the evaluation of compounds present in extracts, as well as the challenge of distinguishing between general cytotoxicity and true antiparasitic activity, the development of new technologies is enabling the discovery and development of new drugs (62). The anthelmintic efficacy of plants can be assessed using various in vitro or in vivo methods. Jato et al. reported that, in their investigation of the anthelmintic activity of medicinal plants, more than 64% of studies used in vitro tests on parasitic and non-parasitic nematode models, evaluating parameters such as the inhibition of egg hatching and larval migration, as well as the paralyzing effect of these plant extracts (58).

In vitro anthelmintic tests

To determine drug efficacy, numerous in vitro methods have been developed for parasitic worms that enable cellular monitoring. These methods include tools based on video image analysis (97), microscopy, metabolic enzymes, fluorescence and impedance (98).

Microscopy

Light microscopy can be used to determine the number of parasites present before and after the administration of an anthelmintic. Electron microscopy can also be used to observe the effects of a plant extract on the membrane of a nematode. For example, in a study by Williams et al., the direct anthelmintic effects of condensed tannins against Ascaris were clearly observed by light microscopy. This was achieved by reducing the migratory capacity of stage three (L3) larvae, which then resulted in increased motility and survival of stage four (L4) larvae recovered from pigs. Using transmission electron microscopy, Williams et al. also reported that condensed tannins caused significant damage to the cuticle and digestive tissues of Ascaris suum larvae (91).

Viability tests

The trypan blue exclusion test is a method for determining the number of viable cells present in a cell suspension (99). This technique is based on the principle that the intact cell membranes of living cells exclude the dye, while the cell membranes of dead cells allow the dye to penetrate. The test is performed by mixing a cell suspension with trypan blue, and then observing the cells under a microscope to determine whether they absorb the dye (blue cytoplasm) or not (clear cytoplasm) (100). Thus, in addition to human cells, the trypan blue viability test can be performed on different types of animal cells, such as mammalian cells and worm cells. This is the case of the trypan blue viability tests carried out on schistosome larvae after culture in 96-well culture plates with the test compounds at various concentrations. Observation under a light microscope enabled the live and dead schistosomules in each well to be counted manually and the 50% inhibitory concentration (IC50) values to be determined (94). Propidium Iodide (PI) is also a cell viability assay based on the principle that intact cell membranes exclude dye from living cells, whereas damaged cell membranes allow the dye to pass into dead cells (99). PI is unique in that it is a fluorescent dye that binds to DNA inside dead cells. Consequently, dead cells are mainly detected and quantified by flow cytometry (101) or fluorescence microscopy, unlike trypan blue, which is observed via light microscopy (102).

Test for larval motility and migration inhibition

This test evaluates the efficacy of a treatment, such as a plant extract or molecule, in causing paralysis and death in larvae. Observations can be macroscopic (visual scoring) or microscopic. A combination of motility and migration inhibition tests is often employed to evaluate the in vitro anthelmintic properties of various compounds against larvae. Williams et al. demonstrated that ten ethanolic plant extracts inhibited the migration of at least 50% of Ascaris suum larvae (74).

Table 1: Plant-derived anthelmintic compounds and their mode of action on worms

Source plants	Active compounds	Categories of metabolites	Target helminths	*In vitro* or *in vivo* activity	References
Acacia cochliacantha (Humb. & Bonpl. ex Willd.)	Caffeic acid, methyl caffeate, methyl p-coumarate, quercetin	Caffeoyl and coumaroyl derivatives	*Haemonchus contortus*	Inhibition of egg hatching	(103)
Aframomum melegueta (K. Schum.)	6 paradol, gingerol, shogaol	Polyphenols, flavonoids, tannins, alkaloids, essential oils	*Litomosoides sigmodontis*	Microfilaricide activity	(104-106)
Ajania nubigena (Wallich ex Candolle)	Luteolin	Flavonoids	*Schistosoma mansoni, Trichuris muris*	Damage the cuticle, bands, and bacillary glands	(107)
Albizia ferruginea (Guill. & Perr.)	Oleanane-type	Saponins, tannins, glycosides, alkaloids, coumarins	*Pheretima posthuma, Haemonchus contortus*	Paralysis and death of worms	(108)
Alectryon oleifolius (Desf.)	Procyanidin A2	Tannins	*Equine cyathostomes*	Inhibition of larval development and migration	(109)
Allium sativum (L.)	Allicin, curcumin	Organosulfur compound, polyphenol	*Schistosoma mansoni*	Reduction in the number of worms and egg load	(110)
Alternanthera sessilis (L.)	Ellagic acid	Tannins	*Haemonchus contortus*	Inhibition of egg hatching and adult worm motility	(88)
Avena sativa (L.)	Avenacoside B, 26-desglucoavenacoside B	Saponins	*Heligmosomoides bakeri*	Morphological changes in larvae, inhibition of glycoprotein pump activity	(111)
Camellia sinensis (L.) Kuntze	Epigallocatechin-(2β→O→7',4β→8')-epicatechin-3'- O - gallate	Polyphenols (Tannin gallate)	*Caenorhabditis elegans*	Toxic activity on oviparous adult worms	(112)
Carica papaya (L.)	Albendazole oxide, 2-Hydroxy-1-(hydroxymethyl)ethyl ester,	Alkaloids, glycosides, flavonoids, saponins, phenols, terpenoids, fatty acid ester	*Allolobophora caliginosa*	Worms' structural changes (reduced size and increased cuticle thickness)	(113)
Chenopodium ambrosioides (L.)	Ascaridole	Essential oil	*Schistosoma mansoni*	Similar anti-schistosomal properties like Praziquantel	(114)

Source plants	Active compounds	Categories of metabolites	Target helminths	*In vitro* or *in vivo* activity	References
Combretum mucronatum (Schu. & Thonn.)	Catechin, epicatechin	Flavonoids and proanthocyanidins	*Ascaris suum, Trichuris suis, caninum*	Inhibition of larval migration	(115)
Corallocarpus epigaeus (Rottler) Hook.f.)	n-Hexadecanoic acid, octadecanoic acid	Lipid (fatty acid)	*Pheretima posthuma*	Paralysis and death of worms	(86)
Cucurbita pepo (L.)	Cucurbitine, berberine, palmatine	Amino acids, alkaloids, fatty acids, nucleosides	*Caenorhabditis elegans* *Heligmosoides bakeri*	Eggs hatching and worm's motility inhibition	(116)
Curtisia dentata (Thunb.) C.A.Sm.	Betulinic acid, lupeol, ursolic acid	Terpénoïdes	*Caenorhabditis elegans* *Haemonchus contortus*	Inhibition of larval motility	(117)
Cymbopogon citratus (DC.) Stapf	Citral	Alkaloids, tannins, steroids, saponins, terpenoids, flavonoids	*Haemonchus placei*	Kill worms	(118)
Indigofera tinctoria (L.)	Degueline	Isoflavonoids	*Haemonchus contortus*	Modulation of oxidative phosphorylation	(119)
Juniperus procera (Hochst. ex Endl.)	Totarol	Terpenoid	*Caenorhabditis elegans*	Nematicidal activity	(120)
Melaleuca alternifolia (Maiden & Betche) Cheel	Terpinen-4-ol	Essential oils	*Haemonchus contortus*	Ovicidal and larvicidal activity	(121)
Momordica charantia (L.)	Momordicins, momordins, momordicosides, caravilagins, caravilosides, kuguacins	Saponins	*Ascaris spp* *Fasciola hepatica* *Strongyloides spp* *Caenorhabditis elegans*	Worms paralysis and death, Inhibition of embryonic development of eggs, Tegument rupture	(122)
Persea americana Mill.	Quercetin, epicatechin	Total phenols, condensed tannins, flavonoids	*Haemonchus contortus*	Larvicidal activity	(123)

Source plants	Active compounds	Categories of metabolites	Target helminths	*In vitro* or *in vivo* activity	References
Piper sylvaticum Roxb.	Piperine	Alkaloids, flavonoids, tannins, and saponins	*Tubifex tubifex*	Paralytic effect on worms comparable to levamisole	(124)
Punica granatum (L.)	5-hydroxymethylfurfural, D-sucrose, sorbitol	Sugars, alcohols	*Strongyloides papillosus*	Larvicidal activity	(125)
Sesbania sesban (L.)	Octadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester	Fatty acids	*Raillietina echinobothrida, Syphacia obvelata*	Damage mouth, suckers, and cuticle/tegument of worms	(126)
Tagetes filifolia (Lagasca)	Chlorogenic acid	Phenolic	*Haemonchus contortus*	Egg hatching inhibition and larvae mortality	(127)
Tetradenia riparia (Hochst.) Codd	8(14),15-Sandaracopimaradiene-7α,18-diol	Diterpene	*Caenorhabditis elegans*	Kill worms	(128)
Thymus vulgaris (L.)	Thymol	Essential oils	*Haemonchus contortus*	Inhibition of egg hatching, larval and adult development	(129)
Tribulus terrestris (L.)	Tribulosin, β-sitostérol-D-glucoside	Steroids, saponins, alkaloids, flavonoids, vitamins, tannins, fatty acids	*Ascaridia galli*	Anti-ascarid activity	(130, 131)
Vernonia amygdalina (Delile)	Vernoniamyoside A–D, vernoamyoside D et vernonioside	Tannins, saponin glycosides, reducing sugars, alkaloids, steroids, flavonoids, terpenoids	*Pheretima posthuma*	Paralysis and death of worms	(132, 133)
Xylopia aethiopica (Dunal) A. Rich.	Xylopic acid (diterpene)	Tannins, saponins, glycosides, flavonoids and alkaloids	*Pheretima posthuma*	Kill worms	(134, 135)

Real-time motility test

xCELLigence a biosensor technology, is an impedance-based technique for real-time analysis of living cells (126) . It enables the continuous monitoring of cell health, behavior, and function. This technology uses custom-made E-plates with gold electrodes to measure electrical changes related to the presence and activity of cells, including growth, migration, proliferation, propagation, cell type, and viability (131). It is a motility-viability test applicable to a variety of helminths (126).

Thus, Wangchuk et al. used the xCELLigence Real-Time Motility Assay for Worms (xWORM) to demonstrate the dual anthelmintic activities of two compounds, luteolin and (3R,6R)-linalool oxide acetate, derived from Ajania nubigena (Wallich ex Candolle), against Trichuris muris and Schistosoma mansoni (94). The xWORM study uses a real-time analysis system, enabling parameters to be optimized and sensitivity to be improved through standardized statistical analysis. This makes the system a valuable platform for measuring drug responses in a multitude of experimental settings (131).

In vivo anthelmintic tests

There are different murine models depending on the species of helminth used for infestation. First, the mice are infested with the appropriate species of helminth. Then, a certain number of days are allowed to pass to allow the infection to manifest. Finally, the models are treated with the plant extracts or compounds of interest. The mice were sacrificed to evaluate the efficacy of the treatment in reducing the number of larvae in the infected groups treated with plant extracts compared to the groups infected and treated with the reference drug (positive control) or infected but not treated (negative control) [132]. Ojo et al. demonstrated that Gongronema latifolium (Benth.) and Picralima nitida (Stapf.) T. Durand & H. Durand exhibited anthelmintic activity in vivo when extracts of these plants were administered to mice, as compared to untreated mice. The 500 mg/kg dose of Picralima nitida extract caused 92.45% chemosuppression in worms, which is comparable to the 92.61% achieved with albendazole [133].

Development of anthelmintic vaccines based on immunogenic plant compounds

Due to helminths' resistance to conventional drugs, developing helminth vaccine antigens based on immunogenic plant compounds is a promising area of research. Nevertheless, one study reported that vaccines against ascariasis and trichocephalosis have been studied through the preclinical testing phase (134). Vaccines against hookworms, onchocerciasis, schistosomiasis, and other geohelminths are in various stages of development (135). Once deployed, these anthelmintic vaccines could be used with anthelmintic drugs in "vaccine-linked chemotherapy" programs to prevent reinfection after MDA (136). In veterinary medicine, a vaccine (TSOL 18) that provides long-lasting control of porcine cysticercosis has been tested in pigs. A control scenario involving vaccination combined with oxfendazole treatment administered at four-month intervals after vaccination proved more effective than the control scenario without vaccination (no pigs slaughtered at 12 months had viable Taenia solium cysticerci) (137).

Conclusion

The growing resistance of helminths to currently available drugs underscore the urgent need to identify and validate novel therapeutic options. Medicinal plants are a promising source of anthelmintic molecules, but the transition from traditional use to evidence-based therapeutics requires more than demonstrating in vitro activity. Future research should prioritize the isolation and structural characterization of bioactive compounds, followed by standardized toxicological assessments and rigorous in vivo and clinical trials to confirm safety and efficacy.

The development of plant-derived anthelmintics should rely on an interdisciplinary approach that bridges pharmacology, ethnobotany, microbiology, public health, and regulatory sciences, extending beyond laboratory research. Strategic collaboration between researchers and traditional healers is crucial to identifying relevant species and safeguarding indigenous knowledge through ethical, mutually beneficial frameworks. Ultimately, promising plant-based molecules can only progress toward becoming affordable anthelmintic drugs and being included in treatment protocols by coupling scientific validation with public health planning. This will allow for their potential integration into community-based parasite control programs. This review contributes to this process by synthesizing current knowledge on anthelmintic drug mechanisms, documenting resistance trends, and highlighting the phytochemical and therapeutic potential of medicinal plants.

Conflict of interest

The authors declared no conflict of interest.

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