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Review article

# Medicinal plants used as anthelmintics: Ethnomedical, pharmacological, and phytochemical studies

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ABSTRACT

Intestinal parasites delay mental and physical development in children. Infection with these parasites can result in complications during pregnancy and alter the health of newborns, which has long-term effects on educational attainment and economic productivity. The appearance of resistance against classical drug treatments generates interest in the development of new deworming alternatives. We think that research of new plants species may reveal potential antiparasitic compounds. This review is focused on the use of plants and secondary metabolites against intestinal parasites. We discuss the use of plants in traditional medicine and the use of plant secondary metabolites tried in *in vitro* and *in vivo* models when available.



**Contents**



## 1. Introduction

According to the World Health Organization, more than 1.5 billion people, or 24% of the world's population, are infected with soil-transmitted helminths (STHs) [1]. Morbidity induced by infection with the major STHs results in an estimated 5.19 million disability-adjusted life years (DALYs) [2]. Infections are widely distributed in tropical and subtropical areas, with the greatest numbers occurring in sub-Saharan Africa, the Americas, China, and East Asia where coinfection with schistosomes and soil-transmitted helminths is common [1].

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The most common and persistent parasitic nematodes that infect humans are the soil-transmitted nematodes—roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), hookworms (*Necator americanus* and *Ancylostoma duodenale*), and thread worms (*Strongyloides stercoralis*)—and the filarial nematodes that are responsible for lymphatic filariasis (LF) (*Brugia sp*. and *Wuchereria bancrofti*) and onchocerciasis (*Onchocerca volvulus*) [3]. The main tapeworms that affect humans are *Taenia solium* and *Taenia saginata* and medium and small tapeworms such as *Hymenolepis nana*, *Hymenolepis disminuta*, and *Dypylidium caninum* [4].

Detrimental health effects caused by intestinal parasites include anemia, impaired cognitive and physical development of children, complications during pregnancy, altered health of newborns, and inflammation [1]. Chronic infections can lead to bladder cancer and have long-term effects on educational attainment and economic productivity. Intestinal parasites disproportionately affect the poorest individuals, particularly in rural areas. Further, in poor and marginalized neighborhoods, infection with these parasites contributes to the cycle of poverty in vulnerable people [5]. It is estimated that 2 billion humans (28% of mankind) are infected with at least 1 species of helminth parasite during some stage of their life [4]. Helminth infection is associated with considerable economic losses in the veterinary world. Studies from developing and developed countries show that the cost of deworming and the health impact of worms on livestock result in major economic losses [5].

Initial contact between host and parasite is during infection, which varies with parasite species. *Strongyloides stercoralis* and *Schistosomes spp*. penetrate the skin actively. Some STHs, including *Angiostrongylus*, infect the host after ingestion of undercooked food, when hands contaminated with soil are put in the mouth, or through an insect vector [6]. The mated state is a fundamental process of parasite viability inside the human host and is necessary for establishing the infection.

Only a handful of anthelmintic compounds are currently available; these are divided into several families that include the benzimidazoles, macrocyclic lactones, imidazothiazoles, and cyclic octadepsipeptides. Targets of these various treatment options are well-documented and include DNA, RNA, cytoskeletal proteins, biomembranes, and the nervous system multicellular host [4]. Host immune determinants (i.e., mechanisms that lead to the killing of the huge multicellular parasite such as filarial nematodes) are currently not well-defined and remain elusive, even though pathways involving the activation of cellular and humoral responses have been described [7]. Moreover, resistance to anthelmintics is concentrated in cities; it has been reported for almost all species of domestic animals and even in some parasites that infect human beings [8]. Studies recently show the presence of gastrointestinal nematodes that are resistant to the main commercially available anthelmintic drugs on cattle farms [9].

Therefore, we consider the research of plants species that may have antiparasitic activity, because many of these plants have been used as medicine in the past [10]. In this review, we discuss the literature examining how plants and their active compounds were used to treat conditions (*in vitro* and *in vivo* effects) consistent with STHs. Further, we review the empirical use of medicinal plants in the treatment of diseases with STH symptomatology.

## 2. Plant species used in ethnomedicine with anthelmintic properties

Approximately 80% of the world's population still relies upon plants for primary health care; even today in Western medicine, and despite progress in synthetic chemistry, approximately 25% of prescription medicines are still derived either directly or indirectly from plants. A trend in phytomedicine is the use of original plant bioactive compounds with the potential for chemical modification, which will broaden phytomedicinal importance [10].

Between 50,000 and 70,000 plants species are used in traditional and modern medicinal methods [10]. Traditional medicine holds great promise as a source of effective treatments, including anthelmintic agents. Traditional medicine is readily available to people, especially in tropical and developing countries [11]. Therefore, plants remain an important aspect of phytochemical studies. The anthelmintic properties of plant species used in traditional medicine is provided in Table S1 of the supporting information.

## 3. Plant extracts characterized in *in vitro* and *in vivo* studies

One potential reason for the limited number of available anthelmintics is the difficulty in identifying lead compounds using high throughput assays. Parasitic nematodes have a complex life cycle with several biological stages (egg, larvae, and adult worm) and adequate experimental systems are not available for every relevant parasite or stage of life. Most reported screens are *in vitro* studies using diverse biological models like *Ascaris lumbricoids, Schistomoma mansoni, Taenia solium*, alternative parasites commonly used for animal relevant helminths (*Haemonchus contortus, Ascaris suum*, and *Taenina crassicep*), and free-living species such as *Pheretima posthuma* and *Caenorhabditis elegans*. The use of *C. elegans* has been instrumental in improving our mechanistic understanding of several antihelmintic compounds [12].

*In vitro* assays are quick to perform and economical compared to *in vivo* tests. Either a single or battery of *in vitro* assays may be employed to prescreen compounds prior to *in vivo* testing. The most frequently used battery consists of a motility assay, an egg hatch inhibition (EHI) assay, a larval development (LD) assay, a larval migration inhibition (LMI) assay, and an assay to measure adult worm viability such as a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) reduction assay. A compound is considered active if it causes complete inhibition of motility and/or >50% inhibition in the MTT reduction assay [13].

A detailed list of plant extracts with anthelmintic activity *in vitro* is provided in Table S2 of the supporting information. Although many researchers report the effectiveness of the extracts differently, we collected and presented 2 measurements: the inhibitory concentration 50 ($IC_{50}$) and the minimum lethal concentration (MLC). We used a cut off effectiveness value of 2000 μg/ml. The most potent extract in Table S2 of the supporting information is from the dichloromethane fruit of *Piper chaba* with a $IC_{50}$ of 0.77 μg/ml against *S. mansoni*. *Piper chaba* is widely distributed in Southeast Asia. The fruit of this plant is commonly called 'Dee Plee' in Thailand and has been used as an anti-flatulent, expectorant, antitussive, antifungal, uterus-contracting agent, sedative-hypnotic, appetite enhancer, anthelmintic, and counterirritant in the traditional medicine of Thailand [14,15]. Moreover, the aqueous acetone extract from the fruit of *Piper chaba* was found to have hepatoprotective effects [16]. Some amides including piperchabamides A-F, piperoleine B, piperanine, piperine, pipernonaline, piperlonguminine, retrofractamides A-C, guineensine, piperchabamides B, E, D, N-isobutyl-(2E,4E)-deca-dienamide, N-isobutyl-(2E,4E)-dodecadienamide, N-isobutyl-(2E,4E,14Z)-eicosatrienamide, and piperchabaosides A and B have been isolated from the methanol extract of the *P. chava* fruit [17,18]. Bornyl piperate, piperlonguminine, and piperine were isolated from the chloroform extract of the *Piper chaba* root. Bornyl piperate and piperlonguminine have been found to possess potent antifungal and cytotoxic activities. Bornyl piperate and piperlonguminine demonstrated weak activity against *Leishmania donovani* promastigotes when compared against the