NEGLECTED TROPICAL DISEASES AND PHYTOCHEMICALS IN DRUG DISCOVERY

EDITED BY
CHUKWUEBUKA EGBUNA | MUHAMMAD AKRAM
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Neglected Tropical Diseases and Phytochemicals in Drug Discovery

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Preface

Neglected tropical diseases (NTDs) represent a group of tropical diseases that are most prevalent in the rural and low-income countries where there are poor healthcare facilities, poor sanitary conditions, and a low standard of living. NTDs affect more than one billion people in both tropical and subtropical regions of the world, causing deaths of over 500 000 people annually while leaving survivors with a lifelong disability. NTDs are so named "neglected" because they often does not get the deserved attention like other diseases such as cancer, diabetes, HIV, COVID-19, and so on. There are about twenty (20) different kinds of NTDs. In this book, an effort was made to capture drug discovery progress and opportunities from medicinal plants and phytochemicals for the treatment of them all. In Part I: Introduction to NTDs, three (3) chapters were dedicated to providing a general overview of NTDs, the disease cycles, and potential druggable targets. In Part II: Protozoan Infections, drug discovery opportunities from medicinal plants and phytochemicals for the treatment of giardiasis, amoebiasis, and leishmaniasis were presented. In Part III: Helminth Infections, five (5) chapters on helminthiasis, human echinococcosis, lymphatic filariasis, dracunculiasis (Guinea worm disease), onchocerciasis (River blindness), and foodborne trematodiases were presented. The chapters provide comprehensive information about the potentials of phytochemicals against helminth infections. In Part IV: Bacterial Infections, four (4) chapters on Buruli ulcer, leprosy, trachoma, and yaws (endemic treponematoses) were presented. In Part V: Viral Infections, two (2) chapters on dengue fever and rabies were presented. In Part VI: Fungal and Ectoparasitic Infections, two (2) chapters on eumycetoma and ectoparasites (scabies and myiasis) were presented while in Part VII: Non-classified NTDs, special chapters were dedicated to malaria and human tuberculosis. In this book, the chapter authors (from key institutions) made a frantic effort to discuss the pathogenic mechanisms of each NTD and the potentials of phytochemicals for their treatment. Well-illustrated diagrams were added and one chapter on a computational approach to drug discovery was added. This book is designed to be useful

to medicinal chemists, drug discovery scientists, students (graduate and post students), and senior academics. This book will also be useful to pharmaceutical industries (R&D) and health institutions such as the World Health Organization. The book editors are grateful to all chapter contributors and are open to receiving feedback and comments from potential users.

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Part I

Introduction to Neglected Tropical Diseases

7

Prospects of Phytochemicals for the Treatment of Helminthiasis

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List of Abbreviations

BLAST	Basic Local Alignment Search Tool
DNA	Deoxyribonucleic acid
IPIs	Intestinal parasitic infections
NCBI	National Centre for Biotechnology Information
QPCR	Quantitative polymerase chain reaction
STH	Soil-transmitted helminthiasis

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7.1 Introduction

Helminthiasis is a common intestinal worm infection found amongst urban and rural populations [1]. From the beginning of human existence, medicinal plants have been used to treat diseases [2–4]. Recently, there has been a growing revival to treat helminthiasis with medicinal plants [5–8]. Various medicinal plants have an ancient history in terms of helminthiasis treatment in traditional systems of medicine. Intestinal worm infections are increasing worldwide. The most serious helminthiasis infections are prevalent in the developing countries, but can also be found across the developed countries. The most common soil-transmitted helminths are parasitic worms from the phyla Nematoda (roundworms) and Platyhelminthes (flatworms); which includes Hookworms (*Ancylostoma duodenale* and *Necator americanus*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*). Approximately 4.5 billion people are at risk of being infected by helminths [9, 10]. All ages are affected by intestinal parasitic infections (IPIs) but children, preschool, and school-going children are the high-risk group and this disease is responsible for poor health and malnutrition. Recurrent infections lead to excess morbidity that can continue from generation to generation in the already poor group of people who are at risk of this disease because of lack of sanitation, lack of access to safe water, and improper hygiene. So, it is most common wherever there are poverty and economic instability [11]. *A. lumbricoides* is the most common helminth and currently infects about 1 billion people worldwide [12]. Figure 7.1 depicts an *Ascaris* worm being removed from a patient's bile duct in South Africa.

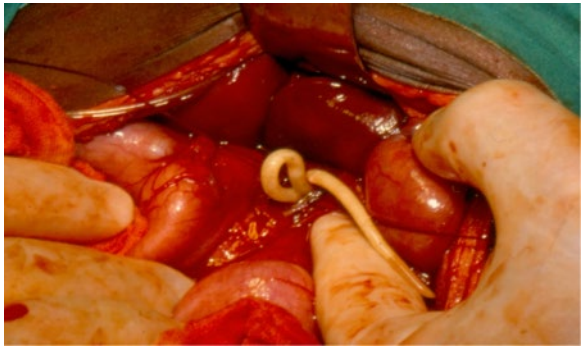

Figure 7.1 Adult *Ascaris* worms being removed from the bile duct of a patient in South Africa. *Source:* Larry Hadley. https://en.wikipedia.org/wiki/Soil-transmitted_helminthiasis#/media/File:Adult_ascaris_worms_being_removed_from_the_bile_duct_of_a_patient_in_South_Africa.png. License under CC AS-BY 2.0.

7.1.1 History

The origin of the word Helminths is Greek which means worms [13]. It has a very old history and has been found in the feces of mummified humans. It has also been described by Hippocrates, Egyptian medical papyri, and in the Bible as infections that have plagued humans since before the era of our earliest recorded history. The eggs of intestinal helminths can be found in the mummified feces of humans dating back thousands of years [1] and can be recognized by the characteristic clinical features of helminth infections from the ancient writings of Hippocrates [1]. The history of treatment with herbal medicine dates back to 3500 years BC and is still widely practiced in India and China which are rich in medicinal plants resources [14].

7.1.2 Prevalence

It is estimated that over 1 billion people in developing regions such as sub-Saharan Africa (SSA), Asia, and the Americas are infected with one or *more* species of helminths [1]. The prevalence noted in Karachi by a study was 52.8%. The most common intestinal parasites were *Giardia lamblia* (28.9%) followed by *A. lumbricoides* (16.5%), *Blastocystis hominis* (10.1%), *Hymenolepis nana* (0.9%), *Endolimax nana* (1.8%), *Entamoeba coli* (2.3%), and *Iodoamoeba butschlii* (3.2%). Coinfection was noted in 43% of samples which comprised of a single parasite while 10% were of multiple parasites [15]. The age group most commonly affected was one to five years of age [12]. Children of preschool age are more affected. There is a high degree of host-parasite tolerance. Roundworms contribute to malnutrition in children and may lead to growth retardation. The prevalence of pinworm infestation is high in children and preschool children of both sexes. Overcrowding, contaminated clothing, and shared bedding favor reinfection and spread. *A. duodenale* is prevalent in Mediterranean countries, Europe, Egypt, and India while *N. Americanus* is prevalent in America and throughout tropical East Africa. Its susceptibility is general, but it is more frequent in Whites than in Negroes. Though some immunity develops with infections, the infected persons remain potential spreaders of infection, so long as they are infected. The common group affected is between 5 and 40 years.

7.2 Molecular Characteristics of Soil-transmitted Helminthiasis

In times past, soil-transmitted helminthiasis (STH) was diagnosed by microscopic examination of stool samples for the presence of the parasites. However, this technique is often regarded to be insensitive. Molecular characterization of STH on

the other hand, begins with the extraction of the DNA from the parasite's eggs or larvae in the sample using a DNA extraction kit for stool or soil samples. In situations where the stool samples cannot be processed at the point (or immediately) of collection, they should be preserved in a solution of potassium dichromate preceding onward transfer to the laboratory for analysis [16]. Quantitative PCR (QPCR) is a viable molecular technique used in the molecular diagnosis of STH. The specific nucleotide sequences (regions) often targeted with respect to diagnosis for STH parasites include internal transcribed spacers 1 and 2 (ITS-1, ITS-2) for primer design usually applicable to all STH parasites (*Strongyloides stercoralis, Necator americanus, Ascaris lumbricoides, Trichuris trichiura,* and *A. duodenale*), while Cytochrome oxidase 1 and/or 5.8S regions are targets in *S. stercoralis, A. duodenale, N. americanus,* and *A. lumbricoides* [16–20]. Having extracted the target regions using the designed primers, QPCR is used for the amplification of these regions with the designated amplification protocol. Amplicons obtained should be sent for sequencing and alignment with existing sequences on the National Centre for Biotechnology Information (NCBI) platform through the Basic Local Alignment Search Tool (BLAST) would be useful for identifying the particular parasite present in the sample.

7.3 Clinical Features and Pathogenesis

The clinical features may vary from being asymptomatic to very vague. Heavy worm infection can cause digestive problems, abdominal pain, diarrhea, vomiting, disturbed sleep, restlessness, and malnutrition [21]. Intestinal obstruction, obstruction of pancreatic and biliary duct, and liver abscess are also known to occur [22–24]. Many times, a live worm in the stool is the first detected sign of roundworm infection. Climate, food preferences, hygiene, and contact with vectors all influence the host's exposure to infection. Host defense mechanisms can eliminate potential infections, but most times once an infection becomes established, it may remain for many years. Sometimes, even infections are asymptomatic while leading to severe pathological changes over time. Worms are large in size and can migrate inside the body causing tissue damage of patients. The host defense mechanism may also damage the body indirectly [25]. Intestinal worms enter the human body via different pathways.

Some intestinal worms such as *Ascaris, Echinococcus, Enterobius,* and *Trichuris* enter by accidental ingestion of contaminated food and water. Other worms may enter the body via the skin. The infected human with mature worms serves as a reservoir for infection of other hosts. The immediate source of infection is the soil containing embryonated eggs. Many helminths affect children than adults, and children living under unhygienic community conditions with a weak immune

system are the most vulnerable. Some children are genetically stronger to resist infection. Lifestyle and dietary conditions may also affect the immune system of the body [26]. Large *Ascaris* can cause blockage in the intestine and bile duct. *Wuchereria* blocks the lymph flow and this condition is called elephantiasis. *Echinococcus granulosus* causes pressure atrophy, a huge fluid-filled cyst. The multilocular hydatid cysts caused by *Echinococcus multilocularis* have a different growth form, migrate to different organs of the body causing widespread damage.

Intestinal worms can produce various abnormalities in the intestinal mucosa, some exhibit physical and chemical damage to the organs, and immunopathologic responses also cause damage to organs. Hookworms known as *Ancylostoma* and *Necator* suck blood from the capillaries of the mucosa. Worms secrete anticoagulants that cause bleeding and blood loss, which leads to anemia and loss of protein. Inflammatory changes occur due to worm infestations which cause protein-losing enteropathies. Vitamin B_{12} deficiency has been observed in patients with roundworm infestations [27].

The skin, lungs, liver, and intestines are most affected sites of the human body. During the migratory phase of worms in the body, some signs and symptoms are produced, including granulomatous lesions, organomegaly, pruritis, pneumonia, petechial hemorrhages, eosinophilia, and urticaria. Worms obtain nutrition from the host, which is the most common etiology of pathogenesis, as evidenced by metaplastic and hyperplastic variations in the epithelium of the host. Hyperplasia in the bile duct epithelium has been observed in association with liver fluke infections. Neoplastic changes may occur due to chronic inflammation caused by some parasitic infection, but the exact etiology is not known. Worms release excretory–secretary materials and cause direct damage to host tissues that are responsible for the pathology [28].

It is alarming that intestinal infections are associated with a degree of immune suppression. Immune suppression has been shown by various factors such as antigen overload, antigenic competition, and induction of suppressor cells, and the production of lymphocyte-specific suppressor factors. Roundworm, fluke or tapeworm may manifest as abdominal pain. Children are particularly susceptible to nutritional deficiencies because of infestations by intestinal roundworms. The poor sanitary facilities, open field defecation, and promiscuous defecation lead to the transmission of roundworm infection. Growth retardation and malnutrition have been observed in ancylostomiasis, strongyloidiasis, trichuriasis, and ascariasis. Severe cases of ancylostomiasis and strongyloidiasis may also cause weight loss. Anemia and fatigue often occur in cases of ancylostomiasis and strongyloidiasis. Cyanocobalamine deficiency has been observed in cases of fish tapeworm (*Diphyllobothrium latum*), which results in hemoglobin deficiency. Fatigue may be a symptom of *fish tapeworm*. Pulmonary eosinophilia occurs due to immature worms present in the lungs. Dry coughing, shortness of breath, fever, chest pain,

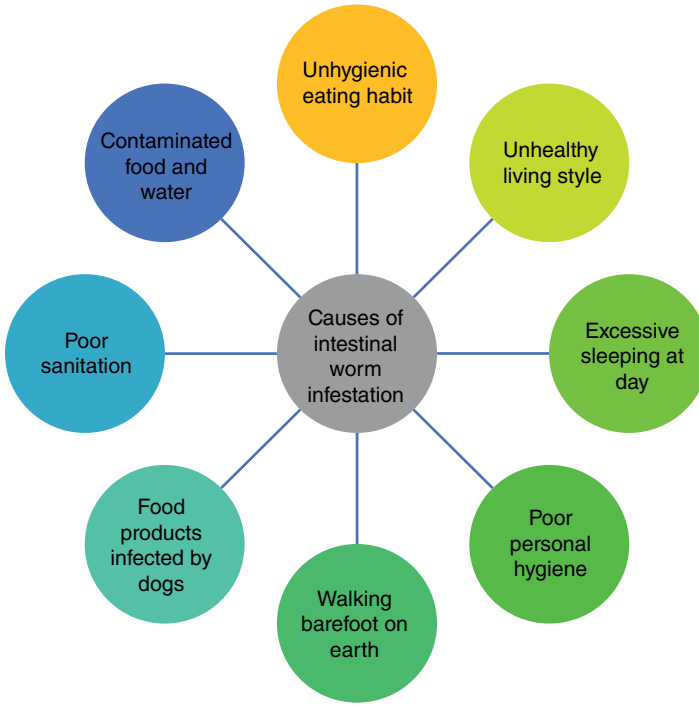

Figure 7.2 Causes of intestinal worm infestation.

and wheezing are often observed in roundworm infestations. Ascariasis is a problem throughout the tropical world and is the major cause of ill health in developing countries. Helminthiasis is prevalent in rural areas of developing countries. Overcrowding and poor housing especially in parasite-favorable climatic conditions keep the transmission rate at high levels (Figure 7.2).

7.4 Prevention

Soil-transmitted helminths are a big source of infection especially in endemic areas and it is difficult to achieve a significant elimination of infection with anthelminthic drugs only so good initiatives should be taken to control the transmission of the disease also along with the morbidity control [29]. Provision should be made for dug well and borehole or any other type of latrines for villagers and persons living in urban areas where there is no facility of private latrines. Vegetables and fruits must be washed, if possible in running water before using

them. Washing hands thoroughly before taking food and after defecation, especially children must follow this rule strictly. Adequate facilities should be made to avoid overflow of ascarid eggs from the drains and latrines, etc. Habits of nail-biting and scratching bare anal area should be discouraged. In selected endemic areas and not in all parts of the world, it is a reportable disease. Vegetables and fruits must be washed properly before eating. Special care is required when these are taken raw. People should have a habit of wearing chappals, shoes and should not go out barefoot. In the endemic region, people must cultivate the habit of washing their feet regularly to prevent infection. Also, programs should be put in place by the healthcare system on educating the masses about the disease and its preventive measures [30].

7.5 Treatment

Anthelmintics are drugs that are used to treat intestinal worms. There are various treatment options that are available in the allopathic system of medicine, but allopathic drugs exert side effects (Table 7.1). A wide number of herbal products are now employed in the treatment of intestinal worms for their purported better efficacy and safety compared to synthetic medicine [37, 38]. Herbal medicine is an integral part of the development of modern civilization. A literature review indicates activities of de-worming drugs that have the potential to treat helminthiasis. The overall findings of the current review show that allopathic drugs and some documented medicinal plants have demonstrable *in vivo/in vitro* anthelmintic activity.

Table 7.1 Side effects of anthelmintic drugs.

Drugs	Side effects	References
Praziquantel	Nausea, vomiting, abdominal pain, giddiness, drowsiness	[31]
Mebendazole	Nausea, vomiting, dizziness, hypotension	[32]
Thiabendazole	Vomiting, diarrhea, anorexia, dizziness, bradycardia, pruritis, rashes, headache, drowsiness, hypotension	[33]
Albendazole	GI disturbance	[34]
Levamisole	Nausea, vomiting, abdominal pain, dizziness, diarrhea, skin rashes, transient neutropenia	[35]
Pyrantel pamoate	Minimal side effects. Neurotoxicity with very large dose, proteinuria	[36]

7.6 Plants and Phytochemicals with Anthelmintic Activities

Some well-known plants validated for their anthelmintic activity are: *Acacia albida*, *Anogeissus leiocarpus*, *Areca catechu*, *Azadirachta indica*, *Bixa orellana*, *Butea frondosa*, *Butea monosperma*, *Caesalpina crista*, *Carica papaya, A. lumbricoides, Carum copticum, Cassia alata, Cucurbita maxima, Cucurbita moschata, Diospyros scabra, Embelica ribes, Hyoscyamus niger, Lagenaria siceraria, Lantana camara, Lansium domensticum, Leucaena lucocephala, Mangifera indica, Melia azedarach, Moringa olefera, Nigella sativa, Peganum harmala, Pisitacia integrrima, Quisqualis indica, Randia dumetorum, Vernonia anthelmintica,* and *Xylopia aethiopica*. The plants commonly used by herbalist as anthelmintic agents are *Bidens pilosa, Tamarindus indica, Combretum collinum, Solanecio mannii, Leonotis nepetifolia, Sclerocarya birrea, Albizia coriaria, Euclea divinorum, Aloe secundiflora, Plectranthus barbatus, Rotheca myricoides, Ximenia Americana, Vernonia amygdalina, Hypitis suaveolens, Erythrina abyssinica, Eclipta prostrate, Cucumis aculeatus, Harrisonia abyssinica, C. papaya, Searsia natalensis,* and *Kigelia africana*. *Ferula assafetida* L. (Apiaceae), *Foeniculum vulgare* (Apiaceae), *Trachyspermum ammi* (Apiaceae), *Calotropis procera* (Asclepiadaceae), *Artemisia brevifolia* (Astraceae), *Brassica campestris* (Bracicaceae), *Matricaria chamomilla* (Astraceae), *Bombax ceiba* (Bumbacaceae), *Eruca sativa* (Bracicaceae), *Aloe vera* (Lillaceae), *Piper nigrum* (Pipreceae), *Withania somnifera* (Solanaceae), *Cuscuta reflexa* (Cuscutaceae), and *Mallotus philippinensis* (Euphorbiaceae) [39].

Phytochemicals are fast gaining attention as alternative sources of therapy in the treatment of helmintic infections. Phytochemicals from medicinal plants (Table 7.2) with proven efficacy in the treatment of STH are usually beneficial to the human body beyond their anthelminthic properties, with negligible side effects when administered within the safe limits. According to [66], *Punica granatum, Clausena anisata,* and *Zanthoxylum zanthoxyloides* are examples of plants containing phytochemicals with anthelminthic activities for the treatment of STH. The various phytochemicals obtained from these plant extracts include alkaloids, terpenes, flavonoids, and tannins. Biocidal activity of Elligatannins from extracts of *P. granatum* against *Cryptosporidium parvum* – a parasitic protozoan has also been reported [67], which is also believed to contribute to the anthelminthic properties of *P. granatum* in the study. Anthelminthic activities of immature fruits of *Magnifera indica* (mango) against *S. stercoralis* were evaluated by [68] as being linked to the presence of tannins in immature mangoes. Other metabolites detected in the immature mango fruit reported are saponins, hydrolyzable tannins, proanthocyanidins, and triterpenes.

Table 7.2 Medicinal plants having anthelmintic activity.

Plant name	Family	Parts used	Chemical constituents	Medicinal uses	Pharmacological activity	References
Carica papaya	*Caricacea*	Seeds, leaves, milky juice, ripe, and unripe fruit	Papain, pectins, carotenoid pigment, carpasemine, carpine, carposide, chemopapain, vitamin C, caricin, protein, carbohydrate, and fatty acids	It is used in stomach ache, dysentery and rheumatism	Digestive, diuretic, anthelmintic, antibacterial, resolvent, antiphlegmatic, antiasthmatic, anti-inflammatory, and antihypertensive	[40, 41]
Butea monosperma Lam	*Fabaceae*	Gums, seeds, flowers, leaves, and bark	Polypeptides, plant proteinase, lipolytic enzymes, proteolytic enzymes, pyrocatecin, mucilaginous material, tannins, gum, phenylalanine, alanine, aspartic acid, histidine, fructose, glucose, lignoceric acid, arachidic acid, palmitic acid, stearic acid, isobutyine, aurones, chalcones, isomonospermoside, monospermide, sulphurine, butin 7 glucoside, isocoreopsin, coreopsin, isobutrin, butin, several flavonoids	It is used in intestinal worms, obesity, fungal infection, cancer, and hyperglycemia	Anthelmintic, antiobesity, antifungal, chemopreventive, and nephroprotective	[42–44]
Baliospermum montanum Muell	*Euphorbiaceae*	Seeds	Montanin, terpenoids, saponins, sterols, glycosides, and flavonoids	It is used in indigestion, urinary tract infection, helminthiasis, inflammation, asthma, constipation, and cancer	Diuretic, purgative, tonic, antiasthmatic, anti-inflammatory, antitumor, antibacterial, anthelmintic, and hepatoprotective	[45]

(*Continued*)

Table 7.2 (Continued)

Plant name	Family	Parts used	Chemical constituents	Medicinal uses	Pharmacological activity	References
Adhatoda vasica	*Acanthaceae*	Flowers, bark, roots, and flowers	Adhatodic acid, vasicinol, vasicine, volatile odorous principle, essential oil, and alkaloids	It is used in asthma, tuberculosis, cough, bronchitis, bronchiectatsis, and lung cancer	Bronchodilator, anthelmintic, and antitussive	[46–48]
Cansjera rheedii	*Opiliaceae*	Aerial parts	Flavonoids, saponins, fats, fixed oils, amino acids, proteins, tannins, steroids, glycosides, carbohydrates, and alkaloids	It is used in helminthiasis	Anti-inflammatory, anthelmintic, antioxidant, and antidiabetic	[49]
Ficus benghalensis	*Moraceaea*	Bark, leaves and seeds	Meso-inositol, tiglic acid ester, furocoumarin, triterpenoids, triterpenes, sterols, flavonol, ketones, glucose, beta sitosterol, 6-heptatriacontene, and tetratriacontene-2-one	It is used in inflammatory bowel disease and helminthiasis	Hypoglycemic, anti-inflammatory, hypolipidemic, antibacterial, immunomodulant, anti-allergic, antipyretic, analgesic, anti-stress, antioxidant, antiatherogenic, growth promoter, ameliorative, wound healer, and antidiarrheal	[50–52]
Rumex abyssinicus	*Polygonaceae*	Aerial parts	Betulone and oleic acid	It is used in inflammation and microbial infections	Antimicrobial, anti-inflammatory, and analgesic, diuretic	[53–55]
Calotropis procera	*Asclepiadaceae*	Roots and leaves	Calotropin, uscharin, calotropagenin, calotoxin, benzoyllineolone, benzoyl isolineolone, syriogenin, beta amyrin, evanidine-3-rhamnoglucoside, *O*-pyrocatechuic acid, urcharidin, uzarigenin, and proceroside	It is used in heminthiasis	Antiasthmatic, antirheumatic, antiseptic, anti-inflammatory, expectorant, antispasmodic, nervine tonic, stomachic, antiphlegmatic, analgesic, diaphoretic, febrifuge, diuretic, anticancer, anthelmintic, and antinociceptive	[56–59]

Plant name	Family	Parts used	Chemical constituents	Medicinal uses	Pharmacological activity	References
Vitex negundo	*Lamiaceae*	Whole plant	Ethyl-hexadecenoate, carryophyllene epoxide, δ-guaiene, (*E*)-nerolidol, germacren-4-ol, α-selinene, β-selinene, hexadecanoic acid, germacrene D, guaia-3, 7-diene, and valencene	It is used in filarial and inflammation	Antimicrobial, anti-inflammatory, antinociceptive, anticonvulsant, and bronchodilator	[39]
Mimosa pudica	*Fabaceae*	Leaves	C-glycosyl flavones, aromatic amino acids, phenolic ketones, flavonoids, alkaloids, and essential oil	It is used in wounds, dysentery and piles	Anthelmintic, hypolipidemic, and antidepressant	[60, 61]
Verbascum thapsus	*Scrophulariaceae*	Aerial parts	Flavonoids, carbohydrates, saponins, tannins, terpenoids, proteins, glycosides, fats, and fixed oils	It is used in cough, asthma, migraine headache, inflammatory diseases, pulmonary problems, and earache	Antiasthmatic, anthelmintic, and antiviral	[62, 63]
Cynodon dactylon	*Poaceae*	Aerial parts	Carotenoids and flavonoids	It is used in diabetes mellitus, cardiovascular disorders, helminthiasis, and cancer	Anti-inflammatory, chemopreventive, antidiabetic, and antiarthritic	[64, 65]

7.6.1 Modes of Action of Phytochemical Against the Soil-transmitted Helminthiasis

For a phytochemical to qualify as an anthelminthic agent, it should successfully target at least one of the stages involved in the life cycle of the helminth. Primarily, this is essential in eradicating the parasite's existence and thereby halting the spread of parasitic infections. The modes of action exhibited by phytochemicals against soil-transmitted helminths as observed are cuticular damage in adult worms, larval development inhibition (LDI), and egg-hatching inhibition (EHI).

Luteolin was reported to be responsible for cuticular damage in adult worms. Tannins were reported to induce EHI and motility in certain stages of larval development of *Haemonchus contortus* [69]. Tannins interact with proteins present in the cuticle of nematode, thereby altering the physical and chemical properties of this region [70]. In a research finding reported by [71], there was 95.7% efficacy of the ethanolic fraction of hexane extract of mango seeds in EHI of *H. contortus*.

7.7 Scientific Reports of Medicinal Plants with Anthelmintic Properties

Some scientific studies have found evidence which is in support of the traditional use of plants against helminths. This section discusses some of these plants.

7.7.1 *Adhatoda vasica*

Adhatoda vasica belongs to the family Acanthaceae. It contains vitexin, quercetin, kaemferol, apigenin, triterpenes, steroids, betaine, vasicolinone, vasicol, and vasicine [72, 73]. Yadav and Tangpu [74] reported the anticestodal activity of *A. vasica* extract against *Hymenolepis diminuta* infections in rats. *A. vasica* is commonly prescribed to treat intestinal worm infestation. Eggs per gram of feces and percentage recovery rates were counted to estimate the efficacy of extract. The extract was administered to rats infected with immature and mature *H. diminuta*. The assay showed that 800 mg/kg double dose of the water extract was effective against mature worms. Eggs per gram count decreased to 79.57%. This efficacy was better than 5 mg/kg of praziquantel, the standard drug used to treat worm infections. There was significant activity against immature worms also. The study indicated that *A. vasica* has anticestodal activity and is useful in intestinal worm infections [74].

7.7.2 *Allium sativum*

Garlic is very rich in selenium. The sulfur compound allicin, produced by crushing or chewing fresh garlic, in turn, produces other sulfur compounds: ajoene,

allyl sulfides, and vinyldithiins [75]. Oil of *Alium sativum* has also been reported to possess anthelmintic activity and expels out the parasites from the intestine [2, 76].

7.7.3 *Baliospermum montanum* Muell

Anthelmintic activity of *Baliospermum montanum* Muell was tested *in vitro* against *Pheretima posthuma* and *Ascardia galli*. The concentration of the drug was 10–100 mg/ml and the time of death and time of paralysis was determined. Significant inhibitory activity was observed at 100 mg/ml of *B. montanum* Muell [77].

7.7.4 *Butea monosperma*

Butea monosperma has antihyperglycemic, anthelmintic, antidiarrheal, wound healer, anticonvulsant, antifungal, anti-inflammatory, hepatoprotective, antistress, and antimicrobial activities [78]. The seeds of *B. monosperma* possess oil, proteolytic and lypolytic enzymes, plant proteinase and polypeptidase, a nitrogenous acidic compound, along with palasonin. The *in vitro* anthelmintic activity of methanolic extract of the seeds of *B. monosperma* has also been reported [79, 80].

7.7.5 *Calotropis procera*

Shivkar and Kumar [81] reported the anthelmintic activity of the latex of *Calotropis procera*. Adult earthworms were used for the assay. Extracts exhibited dose-dependent response. The extract was able to inhibit spontaneous motility (paralysis) and evoked responses to pin-prick [81]. This effect of the extract was comparable to the commonly used drug piperazine, indicating significant anthelmintic activity.

7.7.6 *Carica papaya*

Benzylisothiocyanate present in the seeds of *Carica papaya* is the chief or sole antihelmintic bioactive [82]. Okeniyi et al. [41] reported the effectiveness of dried *C. papaya* seeds against human intestinal parasitosis. For this study, 60 asymptomatic children with intestinal parasites in Nigeria received an elixir (20 ml) of *C. papaya* seeds with honey or honey alone (placebo group) in randomized clinical trials. After seven days of therapeutic intervention, microscopic examination of stool was done to check for the presence of intestinal worms. There was a significantly different degree of reduction of intestinal parasites in

stools of children having received *C. papaya* elixir than those receiving honey alone. No side effects were reported in both treatment groups.

7.7.7 *Ficus benghalensis*

Aswar et al. [83] investigated the anthelmintic activity of petroleum ether, chloroform, water, and methanol extracts of *Ficus benghalensis*. All the extract paralyzed and killed the earthworm.

7.7.8 *Mimosa pudica*

Mimosa pudica belongs to the family Fabaceae. *Mimosa pudica* is also usually recognized as Lajjalu. It is cultivated as a garden plant or grows as a weed in fields. The whole plant is used for medicinal purposes. It is found in India, South and Central America. The water, ethanol, and petroleum ether (100, 200, and 500 mg/kg) of *M. pudica* seeds were investigated for anthelmintic activity against *P. posthuma*. The time of paralysis and death of worms was noted. Normal saline was used as control and albendazole as a standard reference. The aqueous and alcoholic extract caused paralysis and death of worms. The effect of aqueous and alcoholic extract was comparable to the standard and effect of petroleum ether was weaker than standard [84].

7.7.9 *Punica granatum*

Bendgude et al. [85] reported the antihelmintic activity of the pomegranate peel extract of 25, 50, and 75% against *Ascaris suum* females *in vitro*. The 25 and 50% peel extracts were not superior to mebendazole while the 100% was equivalent to it. The chemical constituents responsible for the anthelmintic activity are alkaloids and tannins.

7.7.10 *Verbascum thapsus*

Verbascum thapsus L. belongs to the family Scrophulariaceae. It is an erect biennial plant distributed in all provinces of Pakistan, Kashmir, and Gilgit Baltistan [86]. It contains flavonoids, phenylethanoid glycosides, isocatalpol, aucubin, iridoid, thapsuine, and saponins [87–90]. Ali et al. [91] reported the anthelmintic and relaxant activities of *V. thapsus* Mullein. Anthelmintic activities of this plant were investigated. Crude aqueous methanolic extracts of the plant were used against *Ascaridia galli* and *Raillietina spiralis*. There were two treatment groups. The albendazole treatment group was negative control. Parameters for measurement were time taken for paralysis and death to occur. This extract demonstrated appreciable anthelmintic activity.

7.7.11 *Zingiber officinale*

Zingiber officinale contains shogaols, gingerols, bisabolene, and zingiberene [92]. Up to 1–4% volatile oils are present in the dried rhizome of *Z. officinale*, which are responsible for the characteristic odor and taste and they are also the active constituents of *Z. officinale*. Zingiberene and bisabolene are the aromatic ingredients, while gingerols and shogaols are the pungent compounds [93]. *Z. officinale* possess anthelmintic activity against a wide range of helminthes. The alcoholic extracts of rhizome have good activity against *Ascaris lumbricoldes* [94]. In an *in vitro* study against the adult worm *H. contortus,* the undiluted extracts of *Z. officinale* caused the death of all worms within two hours of the experiment. The total duration of the experiment was 6 hours and observations were noted on 0, 2, 4.6 hours postexposure while the maximum number of worms remained alive in normal saline after 4 hours postexposure [76].

7.8 Future Prospects

A regular and periodic routine of treatment of children below and within the elementary school age and individuals within the at-risk group should be adopted based on the baseline prevalence recorded for these parasites in the various localities. The synthetic drugs of choice include Albendazole which was described by [68], a vermicide that works by keeping the larva from absorbing sugar (glucose), so that the worm loses energy and dies. Mebendazole, levamisole, oxantel pamoate composite, and pyrantel pamoate composite are also drugs of choice. A general mechanism through which these drugs work is by the reduction in egg production of the parasites. However, the shortcoming of synthetic drugs for STH is the increasing rate of drug resistance in parasites. At this juncture, it is important to embrace what nature has in stock through the screening of medicinal plants and phytochemicals which has proven over time that they are the chief source of efficacious chemicals for man's use as food, medicine and other purposes [95–103]. The combined efforts of preventive programs and aggressive search for new lead compounds from medicinal plants will not only help eliminate the tragedies caused by STH, but make life especially those in endemic regions a little better and meaningful. Also, since STH is associated with malnutrition in children, there is need for adequate nutritional intake through proper dieting. Nutritional information on what to recommend is available in the edited book (*Functional Foods and Nutraceuticals – Bioactive Components, Formulations and Innovations*) by Egbuna and Tupas [100].

7.9 Conclusion

The prevalence of intestinal worms in children is rising day-by-day due to poor education and health awareness about the prevention of intestinal worm infestation. Existing approaches to intervene have met with limited success. It is recommended to start a campaign to control intestinal worms by organizing public health seminars, social media campaigns to show the health hazards of unhygienic practices and a focus on improved sanitation, to educate school children and their parents. This should be done on a priority basis to take preventive measures, especially in underdeveloped cities. Personal hygiene and washing of hands after defecation and before eating is necessary. Fingernails of children should be kept clean. Scratching of the perianal area should be avoided. A literature review showed that medicinal plants are effective in the treatment of intestinal worms in children. However, further isolation of active constituents should be done, and the mechanism of action should be studied.

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