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A COMPERHENSIVE REVIEW ON ANTHELMINTIC ACTIVITY

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Abstract:

In the veterinary medicine Anthelmintics drugs are mostly used. We also consider newer anthelmintics, including emodepside, derquantel and tribendimidine. In the absence of vaccines for most parasite species, control of nematode parasites will continue to rely on anthelmintic drugs. As a consequence, vigilance in detecting drug resistance in parasite populations is required. Since resistance development appears almost inevitable, there is a continued and pressing need to fully understand the mode of action of these compounds. Helminthiasis is also known as worm infection, is any macroparasitic disease of humans and other animals in which a part of the body is infected with parasitic worms known as helminths. Anthelmintic agents are medicines that used for treatment and inhibition of parasitic infections caused by helminths; which involve both fl at worms, such as, flukes and tapeworms and round worms, such as, nematodes. Anthelmintics are categorized into groups depending on the basis of their identical chemical structure and mode of action. It is also necessary to identify new drug targets and drugs for the continued effective control of nematode parasites. The remarkable safety record involving more than several hundred million patient exposures over a 20 year period is also documented.

Keywords: Anthelmintic, Benzimidazoles, Avermectins, Vermicide.

Introduction

Helminths or Parasitic worms of humans may cause chronic and sometimes deadly diseases, considered as neglected tropical diseases (NTDs) that infect around two billion people worldwide. Plants have been used as anthelmintics from ancient times. This review is a compilation of plants as source of anthelmintic drug.¹ All information presented in this review article regarding the anthelmintic activities of plants from 2005 and has been acquired by approaching various electronic databases, including Scopus, Google scholar, Web of science and PubMed. Literature was surveyed for anthelmintic activity of plants which showed that secondary metabolites of plants like terpenes, glycosides, saponins, flavonoids, tannins and alkaloids were having anthelmintic activity. Since this review is a compilation of anthelmintic activity of plants from the year 2005, it will definitely be a fruitful study for researchers working in this field. deadly diseases that have a major socio-economic impact worldwide.¹ In humans, the disease caused by the parasitic worms is about 14 million globally, also called neglected tropical diseases (NTD).² In agricultural animals, diseases caused by parasites led to losses of about billions of dollars per year throughout the world.^{3,4c} Gastrointestinal nematodes (GI), such as hookworms, whipworms, and roundworms affected under 15 years most.⁵ Traditionally, the control of GINs has been based on the intensive administration of anthelmintic drugs. However, this has generated anthelmintic resistance, mainly to benzimidazoles and macrocyclic lactones. There are also reports of *Ancylostoma caninum* resistance to pyrantel, *Haemonchus placei* resistance to salicylanilides and imidazothiazoles and cyathostomin resistance to tetrahydropyrimidines³. The situation is exacerbated by multi-resistance to numerous anthelmintics, which has been documented in the aforementioned three genera⁴. The lack of effectiveness of current anthelmintic treatments has prompted the search for control alternatives, including the use of plant extracts with anthelmintic properties and their secondary metabolites. Plant extracts and their natural derivatives have long been used as an additional or alternative treatment to conventional chemical products and have also served as important sources of new anthelmintic molecules for the development of alternative treatments⁵. Among the plants reported to have broad biological activity in the Mexican tropics is *Diospyros anisandra*⁶. found that the bark extract of *D. anisandra* inhibited more than 98% of *Ancylostoma caninum* eclosion (the act of hatching from the egg) in vitro at a concentration 1,200µg/ml and that the leaf extract showed a similar percentage of eclosion inhibition (PEI) at triple the concentration (3,600µg/ml). Thus, the bark extract of *D. anisandra* appears to exert an ovicidal effect. Another study confirmed the effects of the methanolic extract of *D. anisandra* against cyathostomin eggs, finding a PEI > 90% at a concentration of 75µg/ml. Specifically, two effects were noted: an ovicidal effect from using the bark extract and a larval effect using the leaf extract in which larvae failed to hatch (Approximately more than 10% of the population is infected by GI nematodes worldwide deadly diseases that have a major socio-economic impact worldwide.⁸ In humans, the disease caused by the parasitic worms is about 14 million globally, also called neglected tropical diseases (NTD).⁹ In agricultural animals, diseases caused by parasites led to losses of about billions of dollars per year throughout the world.^{3,4} Gastrointestinal nematodes (GI), such as hookworms, whipworms, and roundworms affected under 15 years most.⁵ Approximately more

than 10% of the population is infected by GI nematodes worldwide Indian earthworm *Pheretima posthuma* (Annelida) were collected from the water logged areas of soil, the average size of earthworm being 6-8 cm. They were washed with tap water for the removal of the adhering dirt. Aquarium worms *Tubifex tubifex* (Annelida) were collected from the local market. The average sizes of the worms were 1-1.5 cm. The anthelmintic assay was carried as per the method of Ajayieoba et al¹⁰. with minor modifications. The assay was performed on adult Indian earthworm *Pheretima posthuma*, due to its anatomical and physiological resemblance with the intestinal roundworm parasites of human beings.¹¹ *Pheretima posthuma* worms are easily available and used as a suitable model for screening of anthelmintic drug.¹² The assay was also performed on the aquarium worm, *Tubifex tubifex*, because they belong to same group of Annelida.¹³ *Tamarindus indica* is a tree belonging to the family Caesalpiniaceae whose different parts are used as traditional medicine as analgesic, antiinflammatory, diuretic, febrifuge, and anthelmintic, antifungal and in gastrointestinal problems¹⁴. The anthelmintic activity of leaves has been reported by Sampat et al.¹⁵ but the anthelmintic activity of the bark extracts of *Tamarindus indica* has not been evaluated. Accordingly, this prompted us to investigate the anthelmintic activity of *Tamarindus indica* bark extracts in comparison to the leaf extract.¹⁶ The reference standard drug used in this experiment is piperazine citrate. It causes hyperpolarization of muscle by its GABA agonistic action opening Cl⁻ channels that causes relaxation and depresses responsiveness to contractile action of acetylcholine thereby flaccid paralysis occurs. The worms recover if placed in a piperazine free medium¹⁷. The plant material was collected from the village Amgaon of District Gondia in December during morning hours between 09.00 AM and 10.00 AM. The had-dried leaves and bark were pulverized into coarse particles and extracted with water by maceration (5% chloroform water) and with absolute ethanol using Soxhlet extractor for 72 h. Both the aqueous and alcohol extract were concentrated in a rotary evaporator at a temperature less than 45° and preserved in desiccators for further use. The yield for alcoholic extract and aqueous extract were 49.40% and 47.08%, respectively.¹⁸ The preliminary phytochemical analysis were carried out to find out the phytoconstituents present in the crude extracts.¹⁹

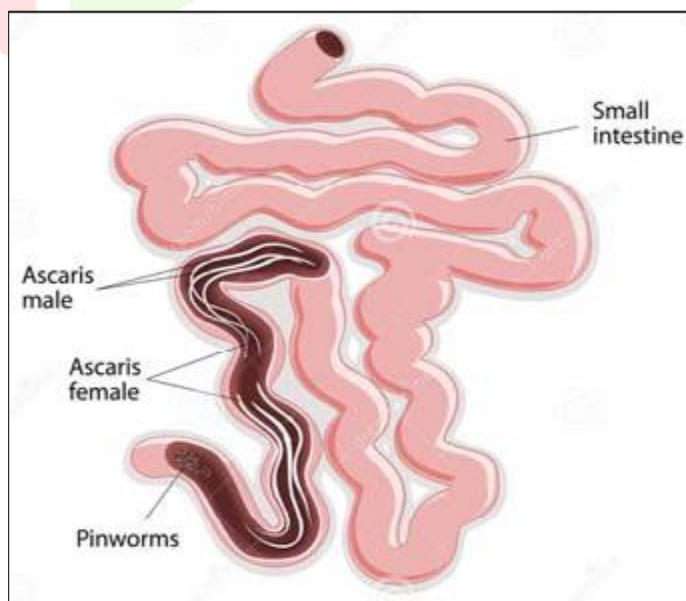


Figure 1: Helminthes.

Phytochemical analysis of the crude extract revealed the presence of tannins along with other chemical constituents contained within them. Tannins have been reported to produce anthelmintic activities²⁰, as they can bind to free proteins in the gastrointestinal tract of host animal or glycoprotein on the cuticle of the parasite and thereby cause deaths²¹. The wormicidal activity of the aqueous and alcohol extract against earthworms suggests that it is effective against parasitic infections of humans. It would be interesting to identify the active principle responsible for the anthelmintic activity and to study its further pharmacological actions.

Tetrahydropyrimidines

Tetrahydropyrimidines share a similar mode of action to imidazothiazoles and are commonly grouped together as nicotinic agonists. Examples of this anthelmintic drug class include pyrantel, oxantel and morantel (Figure 3). Pyrantel is an imidazothiazole-derived tetrahydropyrimidine that was discovered in 1966 as an anthelmintic agent with broad spectrum activity against roundworms and hookworms in domestic animals. Pyrantel however lacks activity against whipworms. Studies on the mode of action of pyrantel at the single-channel level identified the L-subtype nAChR in *A. suum* as also preferentially activated by pyrantel. Pyrantel, like levamisole, also causes open channel-block. Although not characterized at the single-channel UNC-38 and UNC-63 reconstitute a pyrantel/tribendimidine- but not levamisole-sensitive nAChR subtype in *X. laevis* oocytes. The search for an agent with activity against whipworms led to the development of oxantel, an m-oxyphenol derivative of pyrantel. Contrary to pyrantel, oxantel preferentially activates the N-subtype nAChRs in *A. suum*. Oxantel, like levamisole and pyrantel, also causes open channel-block in *A. suum*. Morantel is a methyl ester analog of pyrantel which also targets the L-subtype nAChR in *A. suum*. At the single-channel level, morantel causes the activation and block of this receptor subtype. Recently, morantel was shown to act as an agonist of the nAChR subtype comprising ACR-26/ACR-27 subunits from *H. contortus* or *Parascaris equorum* expressed in *X. laevis* oocytes. In oocyte expression studies, morantel was seen to cause a non-competitive voltage-sensitive open channel block of the newly characterized *A. suum* ACR-16 receptor.

Macrocyclic lactones (MLs)

Macrocyclic lactones (avermectins and milbemycins) are a group of chemical compounds derived from soil microorganisms of the genus *Streptomyces*. MLs were introduced in the 1980s as antiparasitic agents with broad spectrum activity against nematodes and arthropods. Examples of commercially available avermectins are ivermectin, abamectin, doramectin and selamectin, while milbemycin oxime and moxidectin, are examples of commercially available milbemycins. MLs are selective agonists of glutamate-gated chloride channels (GluCl) which are present in neurons and pharyngeal muscles of nematodes and arthropods, but absent in humans. ML activation of GluCl inhibits movement and pharyngeal pumping. In addition to GluCl effects, the avermectins also act as antagonists of 4-aminobutyric acid (GABA) and nicotinic receptors expressed on somatic muscle cells of parasitic nematodes [48–50]. Ivermectin, the first member of the avermectins, although originally developed as a veterinary drug, was later approved for use in humans for the control of onchocerciasis and lymphatic

filariasis. Also, ivermectin was shown to act as an irreversible agonist of recombinant human glycine receptors at higher concentrations ($>0.3 \mu\text{M}$), but at lower concentrations (30 nM), it acted as a positive allosteric modulator. Ivermectin showed a similar positive allosteric modulation effect on the vertebrate neuronal $\alpha 7$ nicotinic acetylcholine receptor .

Discussion

It is interesting to note, that with the exception of the benzimidazoles, the majority of antinematodal drugs act on ion channel proteins in the parasite. Given the number and diversity of predicted channel types in the parasite, it would seem reasonable to focus on these proteins as new drug targets. The success of the macrocyclic lactones led to a hiatus

new drug development to treat nematode infections. Fortunately, the arrival of compounds such as emodepside and derquantel seems to indicate this hiatus is coming to an end. However, the well recognized phenomenon of drug resistance remains a concern. Resistance can be slowed, for example by leaving a refugia of sensitive parasites or by using drug.

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