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A review article on anthelmintic drugs for treatment of parasitic infection caused by helminthes

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ABSTRACT

Anthelmintic drugs are utilized for the treatment of parasitic infection caused by helminths. Roundworms, pinworms, whipworms, hookworms, and tapeworms are all parasitic worms that can invade the body and cause helminthiasis. Antihelmintics with a broad spectrum of activity are effective against nematodes and flat worm parasites. The bulk of medications, however, have more restricted modes of action. Praziquantel, for instance, which is used to treat schistosomiasis and is considered to work by upsetting calcium homeostasis, has no effect on nematodes. Anti-parasitic worm medications are referred to as anthelmintics. This comprises both round worms, such as nematodes, and flat worms, such as flukes and tapeworms. Due to the intimate connection between helminthiases and poverty, their eradication is quite challenging. They are of utmost significance to both veterinary and human tropical medicine. Ascariasis and hookworm infection are caused by helminthinfections.The need for novel and efficacious anthelmintic is vast but little has been done as this disease is mainly associated with poor people of tropical countries. Majority of the countries who suffer from this disease do not have surplus money for drug discovery. The purpose of this article is to summarize the different approaches till date available for treatment of this disease.

KEYWORDS: Helminths, neglected tropical disease, antihelmintic medications, Microtubules, Parasitic infection.

INTRODUCTION

Helminth infections are among the frequently diagnosed problems in developed and developing nations. The number of people who have intestinal nematodes infection is thought to be 2 billion[1-3]. The recent studies revealed that, the number of people who have helminthiasis is rising daily and is thought to affect about half of the global total[4]. Due to close relationship between these diseases and poverty, eradicating helminthiases is extremely difficult. These frequent and widespread infections typically go unnoticed until they start to show symptoms due to the way their clinical development is. They occur more frequently in hot climates, unsanitary environments, and areas where there are large water tanks, parasite carriers, and tainted food and water. This does not imply, however, that prosperous economic circumstances offer full protection from such infections. Individuals from wealthier nations may also contract these infections while visiting areas where they are more common. The majority of the 13 diseases designated as neglected tropical diseases (NTDs) by the WHO are caused by helminth infections, which result in diseases such as ascariasis, hookworm infection, and schistosomiasis[5]. To control parasitic infection brought on by helminths, antihelmintic medications are used[1].

The market is stocked with a variety of anthelmintics, and the parasite can be effectively controlled by using a combination of medications, but the need for new, powerful anthelmintics is great because the chemical drugs currently used to treat helminths are costly yet many end up losing their efficiency after 20 years due to resistance[1, 5]. The value of herbal drugs in medicine has augmented over recent years, which has caused the demand for herbal formulations to increase quickly. As of right now, we only use a few plants to treat anthelmintics, such as Aloe barberi, Trachyspermumammi, and Annonasenegalensis. As vermifuges or vermicides, they go by these names as well. Tobacco, walnut, clove, garlic, pineapple, soya, and other legumes, are some natural anthelmintics that when combined with warm water, act as vermifuges[4].

Antihelminthic chemotherapy is the only feasible, cost-effective method of controlling such infections until efficient vaccines can be developed. The empirical and selective methods have conventionally been used in the search for new anthelmintics[5]. In the empirical approach, numerous chemicals that are completely unrelated to one another and that have not anthelmintic are screened in the hopes that anyone of them will show enough activity to qualify as a chemical lead. Large-scale drug development programmes most frequently employ this technique[6]. The selective approach entails biological analysis of the action of chemicals structurally similar to the ones recognised to have activity against a specific organism. With this strategy, the parent compound is chemically modified with the primary goal of increasing activity or reducing toxicity[1].

1. Classification of anthelmintic drugs:

Anthelmintic activity been obtained from studies on the large parasitic nematodes A. suum, C. elegans, which are utilized in defining molecular targets.

2.1 Benzimidazole

Following the introduction of several additional benzamidazoles as broad spectrum anthelmintics, the first of this class, thiabendazole, was found in 1961. However, it is evident that their ability to disrupt the cytoskeleton through a particular interaction with -tubulin is what gives them their antihelmintic efficacy[7-8]. Antihelmintics containing BZD are extensively metabolised in all mammalian species studied[9]. This class of drugs includes thiabendazole, mebendazole, and albendazole. Microtubule development is hampered by it. The parasite then perishes after losing its cytoskeleton and ability to move. Additionally, it hinders ATP synthesis and glucose uptake. The host's energy metabolism can be disrupted by the BZs, in addition to other mechanisms of action other than tubulin[1].

2.2 Albendazole(ABZ)

Experimentally and clinically, it has been demonstrated that inhibitors of microtubule polymerization have useful antitumor activity. The benzimidazole (BZD) methylcarbamate molecule albendazole (ABZ) has a high level of efficacy against a variety of helminth parasites, including lung worms, adult, and larval stages of the majority of gastrointestinal (GI) nematodes, cestodes, and trematodes According to the findings from clinical trials conducted , albendazole seems to be a potent single dose medication for the treatment of Ascarislumbricoides, Ancylostomaduodenale, Necatoramericanus, Trichuris, and Enterobiusvermicularis. Strongyloidesstercoralis activity was also reduced. Hymenolepis nana and Taeniasaginata, two cestodes, were only moderately responsive to the medication. The eggs of Ascaris, hookworm, and trichuris, as well as the migrating larval stage of N. americanus, were found to be ovicidal[4].

2.3 Thiabendazole

The benzimidazole drugs suppress microtubule formation after binding selectively to β-tubulin in nematodes, cestodes, and flukes. Strongyloidiasis, cutaneous Larva Migrants, and Trichinosis can all be treated with thiabendazole. Microtubular aggregation is impacted by thiabendazole. Thiabendazole, a benzimidazole

compound, is one of the anthelminthics available for the treatment of human strongyloidosis. It is thought to be effective in 75-96% of cases, despite having significant side effects, while albendazole, a treatment alternative, has a cure rate of 42-100%, depending on the dosage regimen and duration of follow-up. There was little understanding of the mechanisms of action of benzimidazoles in echinococcosis at the time, and experimental work was limited. Currently, thiabendazole and its substitute, albendazole, are the only available therapeutic options for the management of human strongyloidosis. But significant side effects from thiabendazole therapy are frequently reported. Better and safer therapeutic alternatives have become necessary as a result of this[1].

2.4 Levamisole, Butamisole, Pyrantel, Morantel, Oxantel, Bephenium and Thenium

Despite being popular and existing in the market for as long as benzimidazole medications, it has been demonstrated that H. contortus has not developed the same level of resistance to levamisole as it has to the benzimidazoles. The tetrahydropyrimidines (pyrantel, morantel, and oxantel), imidazothiazoles (levamisole and butamisole), quaternary ammonium salts (bephenium and theniuna), and tile pyrimidines are some of the other compounds (methyridine). These substances cause contraction and spastic paralysis by selectively acting as agonists at synaptic and extra synaptic nicotinic acetylecholine receptors on nematode muscle cells. Because the excitatory nicotinic acetylcholine (nACh) receptors on body wall muscle are persistently activated by these anthelmintics, which are nicotinic receptor agonists[10-11], spastic muscle paralysis results. On the body wall muscle preparation of A. suum, their precise mode of action has been meticulously studied at the singlechannel level[12]. There are three distinct nACh receptor subtypes, the N-type (preferentially activated by nicotine), the B-type (preferentially activated by bephenium), and the L-type, according to pharmacological analysis[13].

2.5 Pyrantel and its analogues

When applied to the Ascaris muscle, they result in depolarization, increased spike activity, and contraction[11], indicating that these substances have a similar mode of action. pomoatepyrantel Causes helminthes depolarizing paralysis (spastic paralysis). As a result, it is unable to maintain its original position and passes through the stool.

2.6 Macrocyclic Lactones and Milbemycins

2.6.1 Avermectin

A welcome alternative was made possible by the discovery of the avermectins, a group of anthelmintics with a unique chemical makeup. But since they were introduced in the early 1980s, sheep nematodes that are resistant to one of these substances, ivermectin, have been found. The avermectins are a class of broad-spectrum, macrocyclic, lactone antibiotic anthel- mintics used to control nematode parasites in both humans and animals, and are thought to have the same mode of action in both[1, 14].The way avermectins work is by increasing muscle

CI^- permeability, which selectively paralyses the parasite. However, it is unclear which channel the avermectins are targeting. The avermectins cause pharyngeal pumping to be paralysed and increase the opening of glutamate-gated chloride (glucose) channels. Avermectins work by amplifying the effects of glutamate at low concentrations, and at higher concentrations, they directly open the glutamate gated channel[1].

2.6.2 Ivermectin

A derivative of avermectinA called ivermectinlvermectin (22.23-dihydroavermectin Bl) is one of the compounds made by Streptomyces avermitilis[14]. In 1981, it was first used to treat equid internal parasites. Merck first offered ivermectin as an anthelmintic in the 1980s. This substance is a semi-synthetic derivative of avermectin, a large macrocyclic lactone fermentation product produced by the microorganism Streptomyces avermitilis. Insects, acarine parasites, and numerous nematode species are all susceptible to the ivermectin drug. The drug is not active against trematodes and cestodes, according to preliminary tests. In humans, ivermectin has not been tested against gastrointestinal nematodes. Ivermectin is thought to paralyse nematodes and other arthropods by enhancing GABA-mediated signal transmission in the peripheral nervous system. Ivermectin inhibits embryogenesis in onchocerciasis and is a microfilaricidal agent. The pharyngeal and body wall muscles of nematodes are powerfully and persistently paralysed by ivermectin[15-16]. Numerous ligand-gated ion channels, such as the 7 nACh receptors, acetylcholinegated chloride channels, GABA-gated chloride channels, histamine-gated chloride channels, glycine receptors, and P2X4 receptors, have been shown to interact with it. The strong anthelmintic activity of this compound, however, is correlated with its high affinity for nematode glutamate-gated chloride channels (Glucose).

2.7 Other drugs

2.7.1 Amino acetonitrile derivatives and spiroindoles

We are privileged that monepantel (Zolvix®) and a derquantel/abamectin combination (Startect®), the first products in two new anthelmintic classes, the AminoAcetonitrile Derivatives (aads) and the spiroindoles, have been introduced. The need for both parasite control and a sustainability of production necessitate the development of strategies to ensure that the available (old and new) anthelmintics remain as effective as possible. Livestock producers must also be aware of this need. There are undoubtedly a large number of additional compounds in the early stages of development that merit discussion in a piece like the one we're writing right now, but the length constraints of this presentation prevent us from fully exploring their potential. A brief summary of some of these compounds is provided.

2.7.2 Niclosamide

In order to expel tapeworms from the host body, niclosamide, which inversibly damages the proximal segment separating the worms from the intestinal wall, was the drug of choice for tapeworm infections.

2.7.3 Diethylcarbamazine

It is a piperazine derivative that fights filarial infections. According to some theories, it alters the parasite to make it more vulnerable to the host's natural immune responses. Additionally, it might obstruct the parasite's ability to metabolisearachidonate.

2.7.4 Oxamniquine

Both the mature and immature forms of the parasite Schistosomamansoni are impacted by its activity. Its mechanism of action could involve DNA intercalation, and its selective action could be related to the parasite's ability to concentrate the drug.

2.7.5 Praziquantel

Pyrazinoisoquinoline derivatives' anthelmintic properties were discovered in 1972 by E. Merck and Bayer AG. The calcium permeability is increased by praziquantel, which has a specific effect on the trematode tegument. When used against parasitic schistosomes, where its mode of action has been more thoroughly investigated, praziquantel has a selective toxic effect. The majority of medications, however, have more restricted modes of action. Praziquantel, for instance, which is used to treat schistosomiasis and is thought to work by upsetting calcium homeostasis, has no effect on nematodes. The increased Ca "+ permeability of the parasite muscle and/or tegumental membranes may be the cause of many of praziquantel's effects[1].

2.7.6 Paraherquamide

In a membrane preparation that was isolated from C. elegans, a high affinity binding site for paraherquamide was discovered. Parasitic nematodes are paralysed by paraherquamide and its derivative, 2-deoxy-paraherquamide. In vitro experiments using these drugs to study their effects on acetylcholine-stimulated body wall muscle contraction in A. suum revealed that they act as typical competitive antagonists, shifting the concentration-response curves to the right but parallel to one another. Levamisole acts as competitive antagonists rather than cholinomimetics, and paraherquamide was found to be an effective antagonist of the levamisole-selective receptor of the body wall muscle of C. elegans. This indicates that the drug interacts with cholinergic transmission.

2.7.7 Emodepside

The parasite isolates that are defiant to the pore-forming properties of the molecule are successfully combated by it. Given that an optical isomer of emodepside with similar pore-forming properties does not exhibit anthelmintic action, planar lipids do not appear to play a significant role in anthelmintic efficacy. Therefore, it might function by stereospecifically binding to a receptor. The other latrophilin mutants, which react like wild animals, do not exhibit emodepside's inhibitory effect on locomotion. Since emodepside has latrophilin-independent actions, there is no redundancy function in terms of how it affects locomotion as the double mutant responds to emodepside in a similar way. The nine alleles of the gene slo-1 that behave in the same way as the treated animals are recovered by moving 20,000 genomes for mutants and propagating them in micromolar amounts of emodepside, which results in the neuromuscular inhibition.

2.7.8 Nitazoxanide

Numerous protozoa and helminths that live in the intestinal tract are susceptible to nitazoxanide treatment. Nitazoxanide almost completely stops population growth after seven days of culture. Mebendazole and albendazole, in contrast, significantly slowed the growth (by over 90%). Heligmosomoidespolygyrus' embryonation and hatching were unaffected by nitazoxanide. Because of this, this substance's effectiveness is less than that of other anthelmintic drugs[4].

2.9 Natural anthelmintic

The majority of the synthetic anthelmintics are not advised for use in children under the age of six or women who are pregnant due to their toxicity and side effects. The anthelmintic medications are carelessly used to treat parasitic diseases. Therefore, new anthelmintic substances are being developed and discovered using plants as a source. Numerous plants have been used to treat rheumatism, leucorrhoea, dysentery, fever, swellings, abscesses, and venereal diseases[17-18]. They have also been used to promote wound healing. Natural anthelmintic Allium sativum (Lillaceae): Garlic has been shown in vitro to be active against a variety of pathogens, including bacteria, including resistant strains, mycobacterium, Helicobacter pylori, and fungi. Ficusreligiosa (Moraceae)[19], Adhatodavesica (Acanthaceae)[20], Buteamonosperma (Fabaceae)[21-22], and Trichilia emetic (Meliaceae) The extensive traditional use of this species has motivated the scientists to examine several biological activities, including anti-infective, anti-inflammatory, antischistosomal, antiplasmodial, anticonvulsant, antitrypanosomal, antioxidant, antitussive, antimutagenic, and hepatoprotective properties. Moa: Nymania 1 and Trichilia substance Tr-B have growth-regulating, antifungal, bactericidal, antiviral, and selective inhibitory activity toward DNA repair-deficient yeast mutants[1].

CONCLUSION

There are still just a small number of anthelmintic medications on the market today. Because of their restricted range of action, safety concerns, excessive cost, or unworkable delivery systems, many of them are ineffective. Some of these will be terminated as a result of unanticipated issues, such as the emergence of drug resistance, which requires more care than it already does. Before a medicine is ever used in clinical trials, its toxicity, safety, mode of action, and pharmacokinetics must be thoroughly assessed using the most precise quantitative assays. Drug development is expensive, time-consuming, and involves exacting interdisciplinary interactions amongst researchers. All parties involved in the development of new drugs should agree on a set of uniform testing requirements. When creating new chemicals, scientists are starting to use rational design as a strategy. By the continuous efforts made by the scientist by applying rational design to drug discovery the future of Anthelmintic drugs is sensing lucent for the millions of persons suffering from helminthdiseases due to theavailability of broad spectrum compounds which can be utilized in clinics and mass-treatment programs.

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