

Review Article

Anthelmintic agents: vermicide and vermifuge

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Abstract

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 flat 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. Thiabendazole, mebendazole, and albendazole belong to benzimidazoles group of anthelmintic medicines. From benzimidazoles group of anthelmintic, thiabendazole was first discovered in 1961 and already a mentioned number of more benzimidazoles were interpolated as wide spectrum anthelmintics. Praziquantel has a particular effect on the enveloping layer of trematodes and increases permeability of calcium ion influx leading to uncontrolled muscle contraction and paralysis. Praziquantel has a particular toxic effect on schistosome parasites, where its mode of action has been resulted more extensively than in cestodes. Coadministration of mebendazole with CYP450 inhibitors medications such as cimetidine, ketoconazole and etc may be increases plasma levels of mebendazole, by extending the half-life and decreasing plasma clearance.

Introduction

The helminths are invertebrates described by lengthen its flat or round bodies. In medical oriented plot the flatworms or platyhelminths (platy comes from Greek which means "flat") involve flukes and tapeworms [1]. Roundworms are nematodes (nemato comes from the Greek which means "thread"). These classes of helminths are subdivided according to the host organ in which they reside, example, lung flukes, extraintestinal tapeworms, and intestinal roundworms. Helminth infections are the only most present diseases in advancing and advanced countries [2,3]. World Health Organization evaluates that an astonishingly 2 billion people harbour parasitic worm infections and also parasitic worms infect livestock and crops, affecting food production with resulted in economic impacts, and have significant impact on the infection of domestic pets. Assuredly, the escort animal market is a considerable economic deliberation for animal health companies undertaking medicine discovery programmes [4,5].

There are three types of Helminths which are: 1) Nematodes (round worms) involves ascarids (ascaris), filarias, hookworms, pinworms (enterobius), and whipworms (trichuristrichiura), and 2) Cestodes (tape worms) involves

multiple species of flat worms, *taenia saginatum*, *taenia solium* (cysticercosis, hydatid (echinococcus), and 3) Trematodes (flukes) involves liver flukes, lung flukes, schistosoma [6,7] (Figure 1).

Anthelmintic agents

Anthelmintic agents are medicines that are used for treatment of infections with parasitic worms. This involves

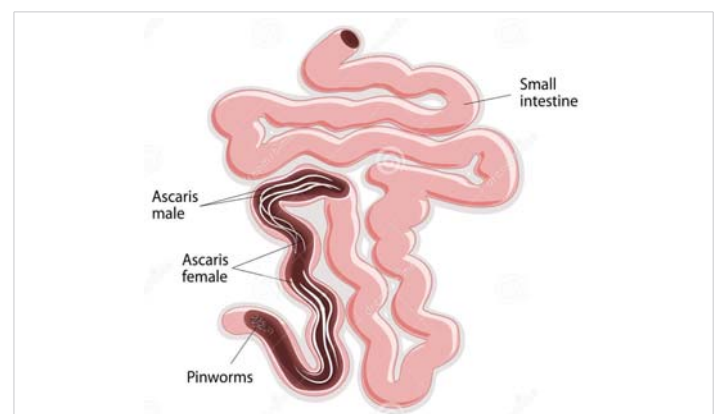


Figure 1: Pictures of type of Helminthes.

More Information

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Keywords: Anthelmintic; Vermicide; Vermifuge

Abbreviations: ADRS: Adverse Drug Reactions; ATP: Adenosine Triphosphate; CYP450: Cytochrome P450; DI: Drug Interaction; GABA: Gamma-Amino Butyric Acid; PFOR: Pyruvate Ferredoxin Oxidoreductase; PH: Potenz Hydrogen; nAChRs: Nicotinic Acetylcholine Receptors; P-gp: Pglycoprotein

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both flat worms, such as, flukes and tapeworms and round worms, such as, nematodes. They have great significance for human tropical medication and for veterinary medicine [8,9]. Anthelmintic drugs are act through two mechanisms: (1) Vermicide (kill) is used to kill parasitic intestinal worms [10]. (2) Vermifuge (eject) is used to destroy or eject worms in the intestine [11]. Albendazole and mebendazole have been selected as concentrated medicine administration programs and have best activity against ascariasis and hookworm infections [12]. Anthelmintic drugs are divided into groups depending on the basis of their identical chemical structure and mode of action [13]. There are only a few pivotal groups of anthelmintic drugs which are briefly discussed in turn below.

Piperazine derivatives (piperazine citrate, diethyl-carbamazine).

Piperazine is an organic compound that consist a six-membered ring containing two nitrogen atoms at opposite positions in the ring [14] (Figure 2).

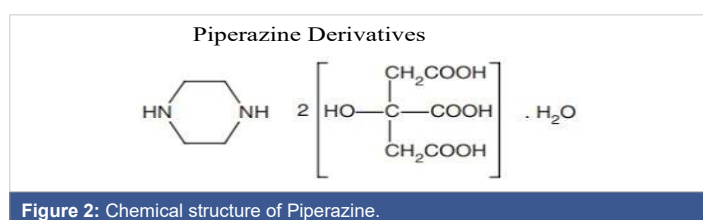
Mechanism of action: Piperazine acts as a weak GABA (4-aminobutyric acid)-mimetic in ascaris summation and causes a flaccid, and reversible paralysis of body wall muscles of helminths. Single-channel recordings of piperazine display a least efficacy and partial agonist at GABA-gated chloride channels and piperazine causes muscle paralysis of the round worm such ascaris lumbricoides as by suppressing the consequences of Ach at the neuromuscular junction [15,16].

Use: Piperazine used for treatment or eradication of roundworms (ascariasis) and pinworm (enterobiasis, oxyuriasis) [17].

Adverse drug reactions: The side effects of piperazine includes bronchospasm; nystagmus; abdominal discomfort; rashes; SJS; angioedema; ataxia, muscular blockage, angioedema, myoclonic contractions, dizziness, paraesthesia [18].

Contraindications: Piperazine is not given to individuals with epilepsy; severe kidney impairment, pregnant women [19].

Drug interactions: If high dose of piperazine and pyrantel coadministered; they have antagonistic effects. If piperazine is administered coincidentally with phenothiazines medications; piperazine potentiates extrapyramidal effects of phenothiazines medications [20].



Benzimidazoles (albendazole, mebendazole, flubendazole, cyclobendazole thiabendazole, fenbendazole, oxi-bendazole, parbendazole)

Benzimidazole is a heterocyclic aromatic compound. This bicyclic compound perhaps viewed as fused rings of the aromatic compounds benzene and imidazole. Benzimidazole is produced by condensation of o-phenylenediamine with formic acid or the equivalent trimethyl orthoformate (Figure 3).

Thiabendazole, mebendazole, and albendazole belong to benzimidazoles group of antihelminthic medicines. From benzimidazoles group of antihelminthic, thiabendazole was first discovered in 1961 and already a mentioned number of more benzimidazoles were interpolated as wide spectrum anthelmintics. BZD anthelmintic drugs are extensively metabolized in all mammalian species is considered [21,22].

Mechanism of action: Benzimidazoles blocks the microtubule formation, then the parasite loses its cytoskeleton, motility eventually dies, and also injures glucose uptakes and decrease production of ATP and also other than tubulin blockage, benzimidazoles ruptures the energy metabolism of the host [23].

Mebendazole

Mebendazole is a derivative of benzimidazole which is made by reacting 3, 4- diaminobenzophenone with N-methoxycarbonyl-S-methylthiourea (Figure 4).

Mechanism of action: Mebendazole acts selectively and irreversibly to inhibits the uptake of glucose and other nutrients, then leading to autolysis and finally cause parasitic worms die [24].

Use: Mebendazole used for treatment of intestinal worm infections caused by pinworm, hookworm and pinworm, *Echinococcus granulosus*; nematode infections; capillariasis [25].

Adverse drug reactions: Mebendazole perhaps cause myelosuppression, gastrointestinal disturbances, headache,

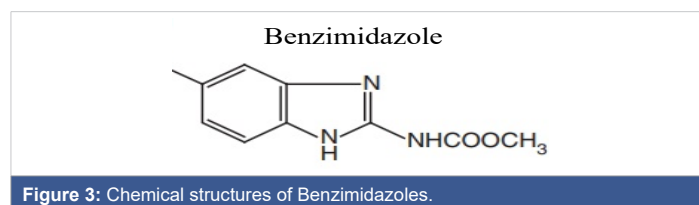


Figure 3: Chemical structures of Benzimidazoles.

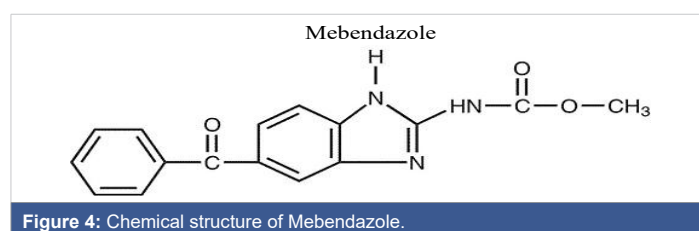


Figure 4: Chemical structure of Mebendazole.

dizziness, with high doses cause allergic reactions, raised liver enzymes, alopecia, numbness, transient diarrhea [26].

Contraindications: Mebendazole contraindicated in pregnant women, for patients who have benzimidazoles hypersensitivity history; for neonates, infants and children less than two years [27].

Drug interactions: Co-administration of mebendazole with CYP450 inhibitors medications such as cimetidine, ketoconazole and etc may increase plasma levels of mebendazole, by extending half-life and decreasing plasma clearance. Concurrent administration of mebendazole with CYP450 inducers medications such as warfarin, phenytoin, carbamazepine etc, decreases the plasma levels of mebendazole by enhancing half-life and increasing plasma clearance [28].

Albendazole

Albendazole is a broad spectrum anthelmintic.

Albendazole, methyl-[5-(propylthio)-1H-benzimidazol-2-yl] carbamate, is made by heterocyclization of a derivative of phenylenediamine to a derivative of benzimidazole [29] (Figure 5).

Mechanism of action: Albendazole acts by inhibiting the glucose uptake of larvae. The adult worm stored exhausts of glycogen thus, decreases the formation of ATP, as a sequence the parasite is immobilized and dies. Albendazole inhibits uptake of glucose and other nutrients, leading to autolysis and death of the parasitic worm [30].

Use: Albendazole used for treatment of a variety of parasitic worm infestations such as giardiasis, Trichuriasis, neurocysticercosis, filariasis, pinworm disease and hydatid disease; *Echinococcus multilocularis*; neurocysticercosis; nematode infections [31].

Adverse drug reactions: Albendazole causes seizures, headache, marrow suppression; yellowing eyes or skin; pregnancy, drug-induced hepatitis, increases in liver enzymes; allergic shock if cyst leakage; convulsions and meningism in cerebral disease; reversible alopecia; rash; and "other" which included spontaneous abortion, change in amount of urine; aplastic anemia; urinary tract infection, motor vehicle accident, dizziness, very stiff neck; fever, vomiting, and intracranial hypertension [32].

Contraindications: Albendazole is not given in pregnant

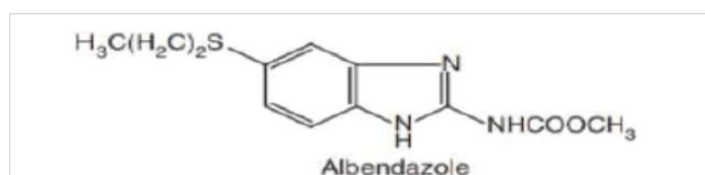


Figure 5: Chemical structure of Albendazole.

women; for patients who have benzimidazoles hypersensitivity history [33].

Drug interactions: If albendazole co-administered with praziquantel, albendazole activity is more effective due to different mechanism of actions, and praziquantel increases the serum concentration of the active metabolite of albendazole [34].

Thiabendazole

Thiabendazole is a broad spectrum anthelmintic.

Thiabendazole is a member of well-known and widely used chemical class of compounds known as the benzimidazoles. It is related in chemical structure and pharmacological properties to other compounds such as fenbendazole, oxbendazole, oxfendazole, febantel or triclabendazole [35] (Figure 6).

Mechanism of action: Thiabendazole prevents the helminth specific mitochondrial enzyme fumarate reductase by suppressing the citric acid cycle, mitochondrial respiration and subsequent production of ATP, eventually leading to helminths death [36].

Use: Thiabendazole is active against strongyloidiasis, cutaneous larva migrans, and trichinosis.

Currently thiabendazole used rarely because of its higher frequency of side effects when compared with other equally active anthelmintic agents from benzimidazole classes. Thiabendazole is used for the treatment of infections caused by worms like threadworm [37].

Imidazothiazole (Levamisole, pyrantel and morantel)

Imidazothiazole consisting of an imidazole ring fused with a thiazole ring has been observed to have excellent immunostimulating and anti-inflammatory activity [38] (Figure 7).

Levamisole

Levamisole is pure L-isomer of tetramisole and levamisole

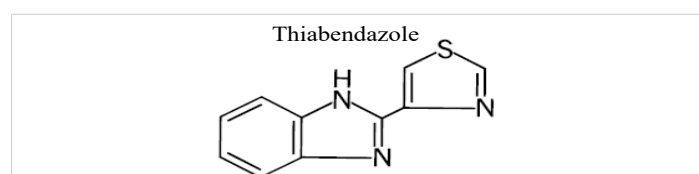


Figure 6: Chemical structure of Thiabendazole.

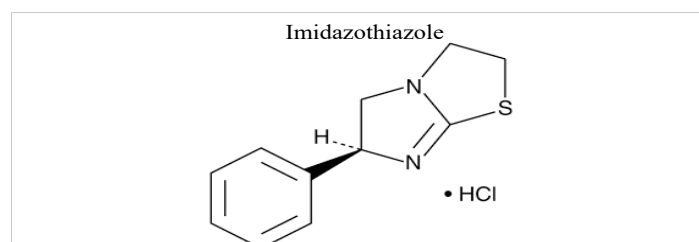


Figure 7: Chemical structure of Imidazothiazole.

has been present on the market as long as the benzimidazole drugs, and has also been widely used, it has been displayed that *H. contortus* has not advanced resistance against levamisole to the identical extent as it has to the benzimidazoles [39].

Mechanism of action: Levamisole additionally act particularly as agonists at synaptic and extra synaptic nicotinic acetylcholine receptors on nematode muscle cells and generate contraction and spastic paralysis by act as nicotinic receptor agonists and reduce spastic muscle paralysis of worms due to extended initiation of the excitatory nicotinic acetylcholine (nACh) receptors on body wall muscle [40].

Use: Levamisole is used for treatment of Ascariasis, hookworm, roundworm and mixed ascariasis with hookworm infections; malignant disease; oral ancylostomiasis [41].

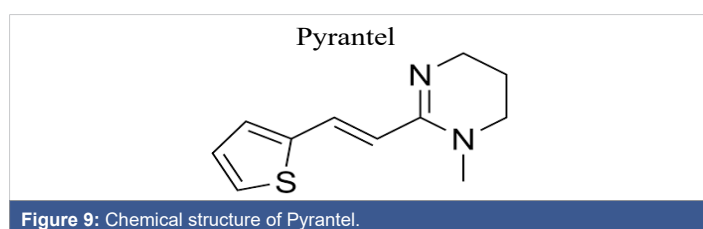
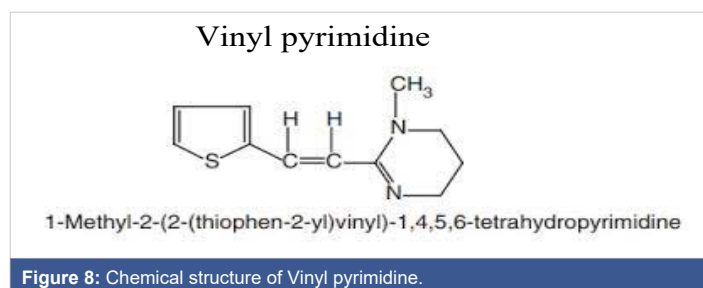
Adverse drug reactions: Levamisole cause abdominal discomfort, nausea, vomiting, influenza like syndrome, taste disturbances, thrombocytopenia, rash, muscle pain; dizziness, and headache; agranulocytosis, leukopenia [42].

Contraindications: Levamisole is not given for nursing mother and pregnant women; individuals with severe kidney impairment; previously blood disorders; rheumatoid arthritis [43].

Drug interactions: If levamisole coincidentally given with antiepileptic medications such as phenytoin; it increases the toxicity of antiepileptic medications such as phenytoin. If levamisole administered with ivermectin, levamisole accelerates the bioavailability of ivermectin [44].

Paraherquamide: Vinyl-pyrimidine (pyrantel, oxantel and its analogues)

PYRANTELPALMOATE- Pyrantel 1, 4, 5, 6-tetrahydro-1-methyl-2-[trans-2-(2-thienyl) vinyl]-pyrimidine is a derivative of tetrahydropyrimidine which is made from 3-(2-thienyl) acrylonitrile from Knoevenagel of furfural with cyanoacetic acid [45] (Figures 8 & 9).



Mechanism of action: Pyrantel is a depolarizing neuromuscular blocking agents and initiates the marked persistent initiation of the nicotinic receptors, which sequence in spastic paralysis of the worm or it generate depolarization, increased spike activity and contraction when functional to ascaris muscle and causes depolarizing type of paralysis (spastic paralysis) of the helminthes [46].

Uses: Pyrantel is used for treatment of ascariasis and enterobiasis, ascariasis, hookworm infections, round worm; pin worm infections; enterobiasis, and trichostrongyliasis; tissue nematode infections [47].

Adverse drug reactions: Pyrantel cause abdominal cramps, headache, insomnia; rash; dizziness, loss of appetite [48].

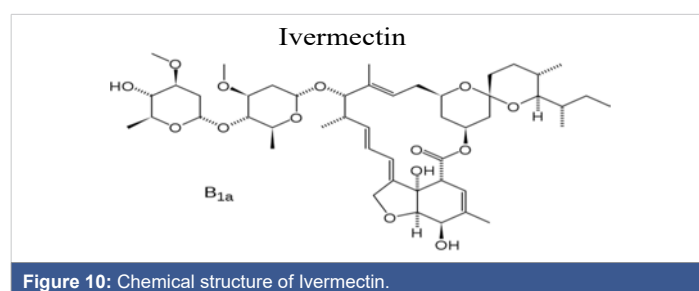
Ivermectin (macrocylic lactones and milbemycins)

Macrocylic lactones (avermectin, ivermectin, abamectin) are generated by the genus streptomyces. They can produce a potent and persistent paralysis of nematode pharyngeal and body wall musculature and have broad-spectrum activity against nematodes. They are specifically agonists of glutamate-gated chloride channels, which are continuing only in invertebrates like nematodes and insects. Besides, avermectins also act as antagonists of GABA and nicotinic receptors concentered on somatic muscle cells of parasitic nematodes [49].

Ivermectin

Ivermectin (22,23-dihydroavermectin B1), a derivative of avermectin A, is a member of the family of substances generated by streptomyces avermitilis. Ivermectin produces a potent and persistent paralysis of nematode pharyngeal and body wall musculature. It has been displayed to interact with a relegate of ligand gated ion channels involving $\alpha 7$ nACh receptors, acetylcholine-gated chloride channels, GABA-gated chloride channels, histamine-gated chloride channels, glycine receptors and P2X4 receptors [50] (Figure 10).

Mechanism of action: Ivermectin selectively binds with great affinity to glutamate-gated chloride ion channels, to increase in the permeability of cell membranes to chloride ion with hyperpolarization of the nerve or muscle cell and ultimately, death of the parasite [51].



Use: Ivermectin indicated for suppressive treatment of onchocerciasis; filariasis; strongyloidiasis; *ascariasis lumbricoides*; scabies [52].

Adverse drug reactions: Ivermectin cause mild ocular irritation; somnolence; raised liver enzymes; rarely postural hypotension; mild Mazzotti reaction within 3 days of treatment, resulting from death of microfilariae, fever, headache, sore throat, cough, pruritus, rash, conjunctivitis, arthralgia, myalgia, lymphadenopathy, lymphadenitis, oedema, weakness, tachycardia, nausea and vomiting, diarrhoea [53].

Contraindications: Ivermectin not indicated for pregnant women and nursing mother; children less than fifty kilogram body weight [54].

Drug interactions: If ivermectin given with alcohol and levamisole, its bioavailability perhaps increased [55].

Emodepside (cyclodepsipeptides, PF1022A)

The molecule has pore-forming properties in planar lipids; however they does not seem to be significant in giving its anthelmintic potency as an optical isomer of emodepside, with identical pore forming properties, does not have anthelmintic action. Thus it would seem that it perhaps function via stereospecific binding to a receptor [56].

Nitazoxanide

Nitazoxanide is a pyruvate ferredoxin oxidoreductase inhibitor that acts against a wide spectrum of protozoa and helminths that happen in the intestinal tract [57].

Mechanism of action: Nitazoxanide interferes with the pyruvate ferredoxin oxidoreductase enzyme dependent electron transfer reaction which is crucial for anaerobic metabolism [58].

Use: Nitazoxanide is recently used for the treatment of protozoal infections; for *C. difficile* associated diarrhea [59].

Adverse drug reactions: Nitazoxanide cause diaphoresis; urine discoloration; allergic reactions; anemia; abdominal discomfort; hypertension; tachycardia; headache, dizziness [60].

Drug interactions: Nitazoxanide perhaps interact with highly protein plasma binding medications such as warfarin, phenytoin, methimazole etc because they compete for the same site of binding.

Praziquantel

The anthelmintic activity of pyrazinoisoquinoline derivatives was discovered jointly by E. Merck and Bayer AG in 1972. Praziquantel has a selective consequence on the enveloping cover of trematodes and increases permeability of calcium ion influx leading to uncontrolled muscle contraction and paralysis. Praziquantel has a selective toxic effect on schistosome parasites, where its mode of action has been considered more extensively than in cestodes [61] (Figure 11).

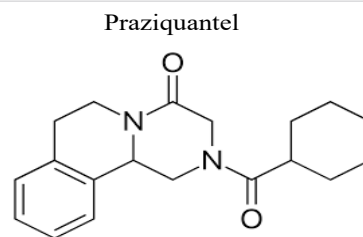


Figure 11: Chemical structure of Praziquantel.

Mechanism of action: Praziquantel act by paralyzing worms' muscular and immobilize their suckers, then cause worms to dislodge from mesenteric veins to the liver, then killed by host tissue reactions or functions by causing strong contractions within the parasite that causes paralysis and eventual dislodgment [62].

Use: Praziquantel indicated for treatment of *Taenia saginata*, *T. solium*, *Hymenolepis nana* and *Diphyllobothrium latum* infections; trematode infections; schistosomiasis; cysticercosis [63].

Adverse drug reactions: Praziquantel cause abdominal discomfort, nausea, vomiting, diarrhoea, malaise; headache, dizziness, drowsiness; rarely hypersensitivity reactions including fever, urticaria, pruritus, eosinophilia (may be due to dead and dying parasites); in neurocysticercosis, headache, hyperthermia, seizures, intracranial hypertension (inflammatory response to dead and dying parasites in CNS) [64].

Contraindications: Praziquantel is not given for individuals who have ocular cysticercosis; hypersensitive patients to the medications and its derivatives [65].

Drug interactions: If praziquantel administered with antibiotic such as rifampicin concurrently; rifampicin decreases plasma concentrations of praziquantel. If Praziquantel is given together with chloroquine, carbamazepine and phenytoin; they decrease the bioavailability of praziquantel. If praziquantel and cimetidine administered concomitantly; cimetidine increases the bioavailability of praziquantel. If praziquantel administrated with dexamethasone, dexamethasone decreases the plasma levels concentrations of praziquantel [66].

Amides (Niclosamide)

Amides have a general structure in which a nitrogen atom is bounded to a carbonyl carbon atom (Figure 12).

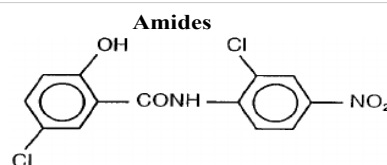


Figure 12: Chemical structures of Amides.

Nicosamide

Nicosamide is a secondary carboxamide resulting from the formal condensation of the carboxy group of 5-chlorosalicylic acid with the amino group of 2-chloro-4-nitroaniline (Figure 13).

Mechanism of action: Nicosamide acts by inhibiting oxidative phosphorylation in mitochondria and interfering with anaerobic production of ATP in tapeworm resulting in energy depletion [67].

Use: Nicosamide is an anthelmintic which is active against most tapeworms, and greatly effective against cestodes infecting man and also used for treatment of fish tapeworm, dwarf tapeworm and beef tapeworm infection; used for treatment of *Taenia saginata*, *T. solium*, *Hymenolepis nana*, and *diphyllobothrium latum* infections [68].

Adverse drug reactions: Nicosamide cause nausea, retching, abdominal pain; lightheadedness; pruritus [69].

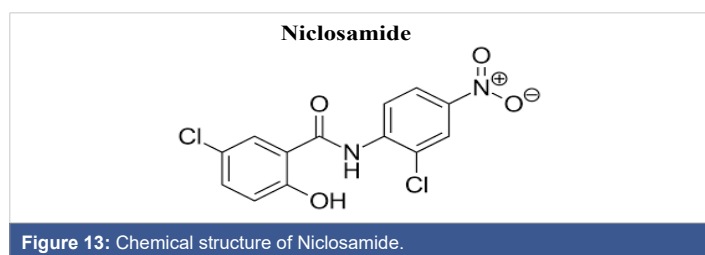


Figure 13: Chemical structure of Nicosamide.

Conclusion

Helminth infections are one of the most frequently occurring diseases in advancing and advanced countries. Albendazole and mebendazole are selected for mass medicine administration programs and most actively used for treatment of ascariasis and hookworm infections. Anthelmintic drugs are divided into some groups depending on the basis of their identical chemical structure and mode of action. Levamisole acts selectively as agonists at synaptic and extra synaptic nicotinic acetylcholine receptors on nematode muscle cells and generate contraction and spastic paralysis. Ivermectin is indicated for suppressive treatment of onchocerciasis; filariasis; strongyloidiasis; *ascariasis lumbricoides*; scabies. If albendazole is coadministered with praziquantel, albendazole activity is more effective due to different mechanism of actions, and praziquantel increases the serum concentration of the active metabolite of albendazole.

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Data Sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, and Cochrane database. Search terms included: anthelmintic agents both vermicide and vermifuge.

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