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Review Article

A REVIEW ON ANTHELMINTIC DRUGS AND THEIR FUTURE SCOPE

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ABSTRACT

The anthelmintic drugs show their effects on the human body and their regular activities by causing helminthiasis which is a very severe parasitic disease. Mostly population and the livestock parasites produce the resistance against the helminths parasites which causes morbidity and mortality. This review deals with the activities of the anthelmintic drugs on the different types of species and on human body also. The prevalence of parasitic worms, anthelmintic drug discovery is more important in the pharmaceutical industry. When the efficacy of available anthelmintic drugs produces the better results over the discovery of new drugs it is hindered by the lack of high-throughput screening methods and drug effect is assessed by observing motility or mortality of parasites using laborious, subjective and low-throughput by using the different genes and mutants. The purpose of this review is to focus on drugs which are used in human and veterinary medicine to treat parasitic nematode infection.

Keywords: Anthelmintic drugs, Herbal drugs, Helminthiasis, Mutants.

INTRODUCTION

Nature has provided a complete store-house of remedies to cure all ailments of mankind and its related diseases. The human being appears to be affected with more diseases than any other animal species. There can be little doubt then that is sought out to alleviate his suffering from injury and disease by taking advantage of plants growing around him. In the past, almost all the medicines used were extracted from the plants and the plant being man's chemist for ages.

The history of herbal medicines is as old as human civilization. The plants were used medicinally in China, India, Egypt and Greece long before the beginning of the Christian era. One of the most famous surviving remnants is Papyrus Ebers, a scroll some 60 feet long and a foot wide, sixteenth century before Christ. The drugs such as acacia, castor oil and fennel are mentioned along with apparent references to such compounds as iron oxide, sodium chloride, sodium carbonate and sulphur. Charaka made fifty groups of ten herbs each of them sufficient for an ordinary physician's need. Sushruta arranged 760 herbs in 7 distinct sets based on some of their common properties[1].

Medicinal plants are the source of great economic value in the Indian subcontinent. Herbal medicine is still the main source of medicine and about 75-80% of the whole population, mainly in developing countries for primary health care because of better cultural acceptability, better compatibility, with the human body and fewer side effects.

Nowadays multiple drug resistance has been developed due to the indiscriminate use of commercial antimicrobial drugs commonly used in the treatment of infectious disease. In addition to this problem, the uses of antibiotics are associated with adverse effects on the host including hypersensitivity, immuno-suppression and allergic reaction. Therefore, there is a need to develop alternative antimicrobial drugs for the treatment of infectious diseases from medicinal plants. Several screening studies have been carried out in different parts of the world. Bacterial resistance is a major medical problem, because it seriously limits the usefulness of many antibiotics. Cross resistance is phenomenon in which bacteria, resistant to one drug are found to be resistant to a second drug without been exposed [2].

Bacterial resistance to antimicrobial drug is either natural or acquired phenomenon. Natural resistance is genetically determined and depends upon the absence of metabolic process or pathway in bacteria which is affected by the antibiotics. Acquired resistance refers to the resistance developed in previously sensitive bacterial species [3]. The biologically active compounds isolated from plant species and used as herbal medicine and plant-based antimicrobials represent a vast source of medicines and further exploration of plant antimicrobials need to be done. Antimicrobials of plant origin have enormous therapeutic potential and are effective in the treatment of infectious diseases while simultaneously mitigating many of the side effects that are often associated with synthetic antimicrobials. Most diseases caused by helminths are chronic, debilitating in nature, they probably cause more morbidity, greater economic and social deprivation among humans and animals than any other parasites. It has been estimated that about half of the world's population suffers from *Helminthiasis* and the number is increasing day by day. It is not only limited to tropical and subtropical countries but is also to endemic in many regions because of poor sanitation, poor family hygiene, malnutrition and crowded living condition [4]. Potent anthelminitics are available today, and treatment is frequently done by using different types of drugs. However the high costs of modern anthelmintics have limited effective control of the parasites. In some cases, wide spread use of low quality anthelmintics are used for the development of resistance and hence causes reduction in use of anthelmintics [5]. Only few of plants are being used traditionally as anthelmintics e.g. *Aloe barberi*, *Trachyspermum ammi, Annona senegalensis* [6].

Herbal drugs and its importance

In the recent years, the importance of Herbal drugs in Medicine has tremendously increased because of their fewer side effects. Consequently, the demand for the herbal formulation is increasing day by day. The phytochemical constituents and their standardization are accelerated with the development of instrumental analysis and this field becomes important and new for investigation.

As the half of world suffering from bacterial and Helminthes infection, the source of infection being very common due to poor sanitation, poor family hygiene, malnutrition, and crowded living conditions[7]. The sources of infections are:

1) Human being: The commonest source of infection is human being themselves.
2) Animals: Many pathogens are able to infect both human being and animals. Animals act as source of human infection.
3) Insects: Blood sucking insect may transmit pathogen to human beings. Besides acting as vector, some insect may also act as a reservoir for hosts.
4) Soil and water: Some pathogens can survive in the soil for very long periods. Water may act as the source of infection either due to contamination with pathogenic microorganism or due to presence of aquatic vector.
5) Food: Contaminated food act as a source of infection [8].

So there is a need to develop antibacterial and anthelmintics drug from herbal source. Anthelmintic activity was carried out by measuring the time for paralysis of worm [9].

Anthelmintic drugs

Helminthes infections are the most common infections in man which affects the large proportions of the world's population. In the treatment of parasitic diseases, the anthelmintics drugs are used indiscriminately. Recently the use of anthelmintics produces toxicity in human beings. Hence the development and discovery of new substances acting as anthelmintics are being derived through plants which are considered to be the best source of bioactive substances. Various plants were used in veneral diseases, to promote healing of wounds, swellings, abscesses, rheumatism and treating pain in lower extremities, skin diseases, leucorrhoea, dysentery, dysuria and fever [10, 11]. Anthelmintics are those drugs that are used in expelling out the worms that are parasitic in nature by either stunning them or by killing them. They are also known as vermifuges or vermicides. Natural anthelmintic includes the following list of components:

- Tobbacco
- Walnut
- Wormwood
- Clove
- Kalonji seeds
- Garlic
- Malefern
- Pineapple
- Diatomaceous earth
- Soya and other legumes
- Honey, water and vinegar are mixed with warm water act as vermifuges.

In other words, anthelmintics are drugs that are used for the treatment of infections caused by the worms, flukes, nematodes, round worms, tapeworms etc. Anthelmintics are the tropical and veterinary types of medicines which are of huge importance. Parasitic worms also infect the livestock and crops thus affecting the food production with a resultant economic impact. It comes as no surprise, that the drugs available for human treatment were first developed as veterinary medicines. In some cases, this situation has been exacerbated by the remarkable success of ivermectin over the last twenty years [12], which has decreased motivation for anthelmintic drug discovery programmes [13]. Broad spectrum anthelmintics are effective against parasitic flat worms and nematodes. However, the majority of drugs are more limited in their action, e.g., praziquantel a drug used in the treatment of schistosomiasis and act by disrupting the calcium homeostasis [14] and has no activity against nematodes.

Pharmacology of anthelmintics

Throughout the world, the parasitic helmintic infection increases the mortality and morbidity day by day. This includes the intestinal nematodes (roundworms), trematodes (flukes) and cestodes (tapeworms). It is unevenly distributed disease in low income countries which affected worstly and highest risk of morbidity because it is the major source of environmental contamination and transmission. Albendazole, mebendazole and praziquantel are the commonly used drugs acting as anthelmintics having broad spectrum activity and high cure rates due to the sustainability of the periodic emergence of resistance.

Roundworms

The migration of the larval forms and eggs transmission through skin contact in moist soil and in tropical areas causes migraine, eosinophilia and pulmonary related problems.

The common infections occurring with intestinal worms include *Ascaris lumbricoides*, *Trichuris trichiura, Necator americanus* and *Ancylostoma duodenal* with the household aggregation of infection. The eggs are deposited on perianal area that is due to self infection. These infections also occur due to the contaminated surfaces like carpets, curtains etc. The airborne and inhalation of the small number of eggs are transmitted through ingestion of the infected food because the humans are the accidental hosts. After the ingestion of the infected products the immunological lungs, liver and central nervous system damages occur.

Flukes

Flukes are the parasitic trematodes of Schistosoma species which are transmitted through direct contact with fresh water. They penetrate into the intact human skin and enter the capillaries and then migrate to the central and portal system where they mature. Acute schistosomiasis also known as Katayama fever, which is a form of visceral larval migraines. The adult male and female pairs ultimately migrate to the superior mesenteric veins and ureteric vesicles. The eggs are then shed in the faeces and urine.

Tapeworms

Humans are the intermediate host for the *Taenia solium* with the development of the tissue cysts. After the ingestion of the uncooked beef (*T. saginata*) or pork it develops the cysts and it causes the mild abdominal symptoms. The infestations of the central nervous systems caused due to the pork tapeworm or flukes are known as neurocysticercosis which is treated through albendazole and praziquantel.

Classes of anthelmintic drugs

Anthelmintics are the broad and wide range of drugs and are separated into classes on the basis of similar chemical structure and mode of action. The physiological and pharmacological actions of anthelmintics have been obtained from studies on the large parasitic nematodes *A. suum*, *C. elegans*, has been used in defining molecular targets.

Piperazine

It is the most popular and readily used drug for the treatment of parasitic infection. Piperazine was first used as an anthelmintic in 1950s and it is still the active constituent as over the counter drug and is used in the remedies for thread worm infection in children. Its mode of action has been studied in *A. suum* and there is no literature survey on its action in *C. elegans* because there is no indication that it acts differently from its effects in A. suum. In *A. suum* it acts as a weak GABA-mimetic agents and this will causes a flaccid or reversible paralysis of body wall muscle.

Benzimidazole

The first thiabendazole was discovered in 1961 and it is a broad spectrum anthelmintics. There is an extensive literature on benzimidazole compounds which showed a number of different biochemical effects. The anthelmintic efficacy of benzimidazoles is due to the ability of compromising the cytoskeleton through a selective interaction with β-tubulin factor [15]. This showed the effects of benzimidazoles on the species of *C. elegans*, which includes the locomotion impairment, reproduction and detrimental effects on oocytes with the disruption of processes thus requires the integral microtubules. Thus the sensitivity of *C. elegans* species gives the response to benzimidazole mediated through a single gene, and encoded by β-tubulin factor [16]. Through this the molecular basis of benzimidazole molecule resistance has been investigated in the parasitic nematodes. The benzimidazole molecule showed resistance in different nematodes like *Haemonchus contortus* which is associated with the presence of specific alleles of β-tubulin in the drug [17]. The specific β-tubulin isoform could confers the resistance for the drug which was tested through experiments but this showed that the sensitivity of *C. elegans* mutants of benzimidazole can be rescued by expressing the *H. contortus* alleles of β-tubulin from benzimidazole through which isolation was done [18]. Through this we demonstrate that a single amino acid substitution, Y for F, in β-tubulin confers the anthelmintic resistance and this is the first example of a 'model hopping' approach.

Levamisole, Pyrantel and Morantel

These anthelmintics are the nicotinic receptor agonist [19] which causes spastic muscle paralysis due to which the prolonged activation of the excitatory nicotinic acetylcholine (nACh) receptors on muscle occurs. The precise mode of action of these receptors has been carefully studied at the single channel level on the body wall muscle preparation of *A. suum* [20]. So the pharmacological analysis has provided evidence for the subtypes of nACh receptors [21]. N-type

receptors are activated by nicotine, B-type of nicotinic receptors is activated by bephenium and an L-type is activated by levamisole and it is associated with levamisole resistance. Levamisole related compounds also causes spastic paralysis in egg-laying *C. elegans*. Recordings from *C. elegans* body wall muscle using levamisole and nicotine as agonist has provided the evidence that there are muscle subtypes of nACh receptor and these subtypes have different receptors subunit compositions. The levimasole receptor subunits are unc-38, unc-29, unc-63 [22]. These anthelmintics provide the pharmacological tools to dissect the subtypes and stoichiometries of native nematode nicotinic receptors. Levamisole has found to been productive in forward genetic screens. The levimasole have provided a resource of mutants that have been used to assign function of genes expressed at the neuromuscular junction. Some of these are nACh (non acetylcholine) receptor subunits, but others interestingly are not and serve to either regulate nicotinic receptors or muscle function.

Paraherquamide

Paraherquamide is a drug of oxindole alkaloid family and marcfortine A are isolated from *Penicillium paraherquei* and *Penicillium roqueforti*, respectively [23]. Marcfortine A was found to be active against *C. Elegans* [24]. The *C. elegans* have high affinity binding site for paraherquamide which has been identified in a membrane preparation which is isolated from *C. elegans*. [25]. Paraherquamide and its derivative, 2-deoxy-paraherquamide, induces flaccid paralysis in parasitic nematodes. Pharmacological analysis is done through *in vitro* tests that showed the effects of these drugs on acetylcholine-stimulated body wall muscle contractions in *A. suum* in which they act as typical competitive antagonists, shifting the concentration-response curves to the right but in a parallel fashion [26]. Paraherquamide also block the action of nicotinic agonists but not equipotently [27]. This antagonist has greater affinity to distinguish the nicotinic receptor subtypes on the muscle but for the receptors mediating the response to levamisole and pyrantel. Paraherquamide was found to be an effective antagonist of the levamisole-selective receptor on *C. elegans* body wall muscle and the mode of action of this drug was to interfere with cholinergic transmission, levamisole, is act as competitive antagonists rather than cholinomimetics. It is a competitive inhibitor of the body wall nACh receptor as it would increase transmitter release.

Ivermectin

Ivermectin is a semi-synthetic derivative of avermectin which is introduced as anthelmintic in the 1980s by Merck contains large macrocyclic lactone fermented product of the micro-organism *Streptomyces avermitilis*. It is a potent drug and its discovery led to the development of ivermectin analogues which include moxidectin, milbemycin oxime, doramectin, selamectin, abamectin and eprinomectin. [28]. Ivermectin causes the paralysis of pharyngeal and body wall musculature [29]. It has been shown to interact with a range of ligand-gated ion channels [30], acetylcholine-gated chloride channels, GABA-gated chloride channels [31], histamine-gated chloride channels [32] and glycine receptors [33]. Nematode glutamate-gated chloride channels (GluCl) has high affinity which is correlated with its potent anthelmintic activity. The Merck team was succeeded in expressing the cloning of GluCl-α and GluCl-β ion channel subunits in *C. elegans* [34] but both subunits were expressed either singly or together. GluCl-α responds to micromolar quantity of ivermectin, but not to glutamate while GluCl-β responds to glutamate but not to ivermectin because co-expression of GluCl-α and GluCl-β yields a channel which responds to glutamate and it is positively but allosterically modulated by nano-molar quantity of ivermectin [35]. Essentially there are four genes of *C. elegans* which are encoded by GluCl-α subunits, two of which are alternately spliced the GluCl channels. The pharyngeal muscle of mutants of avermectin species does not respond to ivermectin [36]. Ivermectin anthelmintic activity against *Ascaridia galli* and the pharynx of this species is not inhibited by this drug [37]. The role of GluCl channels in mediating the paralytic actions of ivermectin is playing an important role in the motor nervous system. There is an immuno staining role of GluCl-α3 A and B in motor neurons of the parasitic nematode *H. contortus* [38]. The role of these GluCl channels in *C. elegans* involves the regulation of the duration of forward movement and glutamatergic regulated behaviour [39]. The paralytic action of ivermectin derives from activation of GluCl in the motor nervous system of nematodes. The mechanism of ivermectin resistance has been well studied in *C. Elegans* because high level of resistance is required in mutations of these species. These genes further regulate the membrane permeability and gap junctions [40]. The role of GluCl mutations in conferring ivermectin resistance of parasitic nematodes in the field is a less tractable and more controversial [41].

Emodepside

Emodepside is cyclodepsipeptide molecule and semi-synthetic derivative. A product obtained through fermentation from the fungus, *Mycelia sterilia*. Its discovery and anthelmintic activity has recently been discovered [42]. It is effective against isolates of parasites that are resistant to the molecule having pore-forming properties. Planar lipids does not appear to be an important in anthelmintic potency, as an optical isomer of emodepside with similar pore forming properties does not shows anthelmintic action. Thus it may act through the stereo specific binding to a receptor. *A. suum* causes the muscle paralysis and have calcium and potassium dependent mechanism of action [43].The receptors for the cyclodepsipeptides have been cloned from a *H. contortus* cDNA library by immuno screening with an antibody. This receptor has been designated in the cells and showed gate calcium flux in a dependent manner [44]. Its homology is like mammalian latrophilins, which is a class of G protein-coupled receptors which bind to the neurotoxin, latrotoxin. Latrotoxin paralyze the mammals by triggering neurotransmitter release and thus the identification of latrophilin as an emodepside receptor raised the possibility that emodepside causes paralysis by stimulating excessive neurotransmitter release at neuromuscular sites thus showing effects such as slowed development, inhibition of pharyngeal pumping, decreased locomotion and inhibition of egg-laying in adult hermaphrodites which showed that emodepside exerts its pleiotropic actions. The use of the latrophilins in mediating the inhibitory effects of emodepside showed its effects on feeding and locomotion using RNA and genes [45]. The pharyngeal system of mutants showed a reduced sensitivity in the favor of emodepside but its locomotors activity is inhibited [46]. Emodepside does not show its inhibitory effect on locomotion through the other latrophilins mutants which respond just like wild animals. There is no redundancy function in terms of effect of emodepside on locomotion, as the double mutant's responds to emodepside in a similar fashion [47] because emodepside has latrophilin-independent actions. Twenty thousand genomes for mutants are moved and propagates in micromolar quantity of emodepside recovered the nine alleles of the gene named slo-1. There is an inhibitory effect on the locomotion and feeding by emodepside carrying the null alleles. Emodepside activates the slo-1 gene which behaves in the same manner as the treated animals thus bring about the neuromuscular inhibition.

Nitazoxanide

Nitazoxanide is a pyruvate ferredoxin oxidoreductase inhibitor which acts against broad spectrum of protozoa and helminths that occur in the intestinal tract. It is currently used for the treatment of protozoal infections. The mechanism of action of this compound has not been found in nematodes because anaerobic electron transport enzymes are the potential target [48]. After seven days of culture, nitazoxanide reduces population growth by 33%. In contrast mebendazole and albendazole reduced the growth by over 90%. Nitazoxanide had no effect on either embryonation or hatching in *Heligmosomoides polygyrus*. Therefore the efficacy of this compound is relatively low as compared to other anthelmintic agents.

FUTURE SCOPE OF THE ANTHELMINTIC DRUGS

The challenges for the companies that are engaged in anthelmintic behavior of the drugs are not shared by wealthy phase in the pharmaceutical industry because anthelmintic drugs market is cost-effective and it is a prime concern. For mostly tropical medicine anthelmintics must be used in chemotherapy programmes in those regions where clinical support is sparse and then drugs need to be

very well tolerated in humans. For the last twenty years a small quantity of drugs, especially ivermectin has addressed the need whereas ivermectin has been hugely successful both in veterinary and tropical medicine. The widest concern for the future is the emergence of resistance to all the anthelmintics that are used currently including ivermectin a pivotal in defining the mode of action for the majority of these drugs and can also contribute in understanding mechanisms of resistance especially through the 'model-hopping' approach. In future it is to be hoped that new anthelmintics that have novel modes of action will solve the problem of anthelmintic resistance. More targeted approaches to anthelmintic drug discovery are also ongoing and thus providing the fundamental information with the aim not to target peptidergic signaling pathways which translated a marketable drug [49]. The future holds the promise that *C. elegans* may also directly contribute to drug discovery and efforts are of utmost importance in view of the increasing threat to live-stock and humans from anthelmintic resistance.

CONCLUSION

From this review it is concluded that anthelminitic activity of some drugs was based on its resistant activity and helminthiasis causing considerable hard hip and stunted growth. Mostly disease caused by Helminthiasis is of chronic debilitating and of severe nature which causes more morbidity. It is concluded that the anthelmintic efficacy of certain drugs might be attributed in the presence of genes, phytochemicals and mutants. The tropical medicines are mainly used in the treatment of this severe disease. The Anthelmintics drug treatment must be used in chemotherapy programmes in those regions where clinical support is sparse and where drugs are very well tolerated in humans. For the last few years a small quantity of drugs, especially ivermectin, albendazole, piperazine, emodepside has addressed the need whereas ivermectin has been hugely successful both in veterinary and tropical medicine.

REFERENCES

1. Kokate CK, Purohit AK, Gokhale SB. History, definition and scope of Pharmacognosy. Pharmacognosy 2005. p 1-14.
2. Parekh J, Darshana J, Sumitra C. Efficacy of Aqueous and Ethanol Extracts of some Medicinal Plants for Potential Antibacterial Activity. Turk J Biol 2005; 29: 203-210.
3. Barar FSK. Essential of Pharmacotherapeutics. 2000. p. 347-453.
4. Mohammed MS, Mohammed M, Yusuf OA, Joseph OA. Anthelmintic activity of the crude methanol extracts of *Xylopia aethiopica* against *Nippostrongylus brasiliensis* in rats. Veterinarski Arhiv 2005; 75: 487-495.
5. Barar FSK, Essential of Pharmacotherapeutics. 2000. p. 347-453.
6. Ibrahim MA, Nwude N, Ogunsusi RA, Allu YO. A paper presented at the 5th International Symposium on Medicinal plants, University of lfe, lle-lfe, Nigeria; 1983. p.13-15.
7. Basu and Sharma. Tropical gardening plant in India. 2005.p. 17-18
8. Ananthnarayan V, Thomson C. Structure function studies on Hsp47: pH dependent inhibition of collagen. J Biochem 2000; 349: 877-83.
9. Mohammed MS, Mohammed M, Yusuf OA, Joseph OA. Anthelmintic activities of the crude methanol extract of *Xylopia aethiopica* against *Nippostrongylus brasiliensis* in rats**.** Veterinarski Arhiv 2005; 75:487-495.
10. Anisuzzaman M, Rahman AHMM, Harun-or-Rashid M, Naderuzzaman ATM, Islam AKMR an Ethnobotanical Study of Mdahupur, Tangail. J App Sci Research 2007; 3: 519-530.
11. Vijayan A, Liju VB, Reena John JV, Parthipan B, Renekac. Traditional remedies of kani tribes of kotor reserve forest, Agasthyavanam, Thiruvanathapuram kerala. Ind. J Trad Know 2007; 6 : 589-594.
12. Geary TG. Ivermectin 20 years on maturation of a wonder drug. Trends Parasitol 2005; 21: 530–532.
13. Geary TG, Sangster, NC, Thompson, DP. Frontiers in anthelmintic pharmacology. Vet Parasitol 1999; 84: 275–295.
14. Greenberg RM. Ca^{2+} signaling, voltage-gated Ca^{2+} channels and praziquantel in flatworm neuromusculature. Parasitol 2005; 131: S97–S108.
15. Borgers M, De Nollin S. Ultra structural changes in *Ascaris suum* intestine after mebendazole treatment *in vivo*. J Parasitol 1975; 61: 110–122.
16. Driscoll M, Dean, E, Reilly E, Bergholz, E, Chalfie M. Genetic and molecular analysis of a *Caenorhabditis elegans* beta-tubulin that conveys benzimidazole sensitivity. J Cell Biol 1989; 109: 2993–3003.
17. Kwa M.S, Veenstra, JG, Roos M H. Benzimidazole resistance in *Haemonchus contortus* is correlated with a conserved mutation at amino acid 200 in beta-tubulin isotype. Mol. Biochem Parasitol 1994; 63*:* 299–303.
18. Kwa MS, Veenstra JG, Van D M., Roos, M.H. Beta-tubulin genes from the parasitic nematode *Haemonchus contortus* modulate drug resistance in *Caenorhabditis elegans*. J. Mol Biol 1995; 246*:*500–510.
19. Aceves J, Erlij D, Martinez-Maranon, R. The mechanism of the paralyzing action of tetramisole on *Ascaris* somatic muscle. Br J Pharmacol 1970; 38: 602–607.
20. Martin, R.J, Verma S, Levandoski M, Clark C L, Qian H, Stewart M., Robertson A P. Drug resistance and neurotransmitter receptors of nematodes: recent studies on the mode of action of levamisole. Parasitol 2005; 131: S71–S84.
21. Qian H, Martin RJ, Robertson AP. Pharmacology of N-, L-, and B-subtypes of nematode nAChR resolved at the single-channel level in *Ascaris suum*. FASEB J 2006; 20*:*2606–2608.
22. Culetto E, Baylis HA, Richmond JE, Jones AK, Fleming JT, Squire MD, Lewis JA, Sattelle, DB. The *Caenorhabditis elegans* gene encodes a levamisole-sensitive nicotinic acetylcholine receptor alpha subunit. J Biol Chem.2004; 279: 42476–42483. Rand JB. Acetylcholine. Worm Book ed 2007 .The *C. elegans* Research Community, WormBook, doi/10.1895/wormbook.
23. Zinser EW, Wolfe ML, Alexander BSJ, Thomas EM, Davis JP, Groppi VE, Lee BH,et al. Anthelmintic paraherquamides are cholinergic antagonists in gastrointestinal nematodes and mammals. J Vet Pharmacol Therapy 2002; 25: 241–250.
24. Lee BH, Clothier MF, Dutton FE, Nelson SJ, Johnson SS, Thompson DP, et al. Marcfortine and Paraherquamide class of anthelmintics: Discovery of PNU-141962. Curr. Top. Med. Chem.2002; 2: 779–793.
25. Schaeffer JM, Blizzard TA, Ondeyka J, Goegelman R, Sinclair PJ, Mrozik H. [^{3}H]-Paraherquamide binding to *Caenorhabditis elegans*. Studies on a potent new anthelmintic agent. Biochem Pharmacol 1992; 43: 679–684.
26. Robertson AP, Clark C.L, Burns TA, Thompson DP, Geary TG, Trailovic SM, Martin RJ. Paraherquamide and 2-deoxy-paraherquamide distinguish cholinergic receptor subtypes in *Ascaris* muscle. J Pharmacol Exp Ther 2002; 302; 853–860.
27. Zinser EW, Wolfe ML, Alexander B SJ, Thomas EM, Davis JP, Groppi VE, et al. Anthelmintic paraherquamides are cholinergic antagonists in gastrointestinal nematodes and mammals. J Vet Pharmacol Therap 2002; 25:241–250.
28. Haber CL, Heckaman C L, Li GP, Thompson DP, Whaley HA, Wiley VH. Development of a mechanism of action-based screen for anthelmintic microbial metabolites with avermectin-like activity and isolation of milbemycin-producing *Streptomyces* strains. Antimicrob Agents. Chemother 1991; 35: 1811–1817.
29. Brownlee DJ, Holden-D L, Walker RJ. (1997). Action of the anthelmintic ivermectin on the pharyngeal muscle of the parasitic nematode, *Ascaris suum*. Parasitology.1997; 115; 553–561. Pemberton DJ, Franks CJ, Walker RJ, Holden DL. Characterization of glutamate-gated chloride channels in the pharynx of wild-type and mutant *Caenorhabditis elegans* delineates the role of the subunit GluCl-alpha2 in the function of the native receptor. Mol Pharmacol 2001; 59:1037–1043.
30. Krause RM, Buisson B, Bertrand S, Corringer PJ, Galzi JL, Changeux JP, et al. Ivermectin: a positive allosteric effector of the alpha7 neuronal nicotinic acetylcholine receptor. Mol Pharmacol 1998; 53: 283–294.
31. Bokisch AJ, Walker RJ. The action of Avermectin (MK 936) on identified central neurones from *Helix* and its interaction with acetylcholine and gamma-aminobutyric acid (GABA) responses. Comp. Biochem. Physiol C Comp Pharmacol 1986; 84:119–125. Holden-DL, Walker RJ. Avermectin and avermectin derivatives are antagonists at the 4-aminobutyric

acid (GABA) receptor on the somatic muscle cells of *Ascaris*; is the site of anthelmintic action. Parasitol 1990; 101: 265–271.

32. Zheng Y, Hirschberg B, Yuan J, Wang AP, Hunt DC, Ludmerer SW, et al. Identification of two novel *Drosophila melanogaster* histamine-gated chloride channel subunits expressed in the eye. J Biol Chem 2002; 277: 2000–2005.
33. Shan, Q, Haddrill JL, Lynch JW. Ivermectin, an unconventional agonist of the glycine receptor chloride channel. J Biol Chem 2001; 276: 12556–12564.
34. Cully DF, Vassilatis DK, Liu KK, Paress PS, Van der Ploeg LH, Schaeffer JM, et al. Cloning of an avermectin-sensitive glutamate-gated chloride channel from *Caenorhabditis elegans*. Nature 1994; 371: 707–711.
35. Yates DM, Portillo V, Wolstenholme AJ. The avermectin receptors of *Haemonchus contortus* and *Caenorhabditis elegans*. Int J Parasitol 2003; 33: 1183–1193.
36. Dent JA, Davis MW, Avery L. Encodes a chloride channel subunit that mediates inhibitory glutamatergic neurotransmission and ivermectin sensitivity in *Caenorhabditis elegans*. EMBO J 1997; 16: 5867–5879.
37. Holden D L, Walker R J.Actions of glutamate and ivermectin on the pharyngeal muscle of *Ascaridia galli*: a comparative study with *Caenorhabditis elegans*. Int J Parasitol 2006;36: 395–402.
38. Portillo V, Jagannathan S, Wolstenholme AJ. Distribution of glutamate-gated chloride channel subunits in the parasitic nematode *Haemonchus contortus*. J Comp Neurol 2003; 462: 213–222.
39. Brockie PJ, Maricq, AV. Ionotropic glutamate receptors: genetics, behavior and electrophysiology, Worm Book ed. The *C. elegans* Research Community, 2006; WormBook, doi/10.1895/wormbook.
40. Dent JA, Smith MM, Vassilatis DK, Avery L. The genetics of ivermectin resistance in *Caenorhabditis elegans*. Proc Nat Acad Sci U.S.A 2000; 97: 2674–2679.
41. Wolstenholme A J, Fairweather I, Prichard R, Himmelstjerna, VSG, Sangster NC. (2004). Drug resistance in veterinary helminths. Trends Parasitol 2004; 20: 469–476.
42. Harder A, Himmelstjerna V S G. Cyclooctadepsipeptides a new class of anthelmintically active compounds. Parasitol Res 2002; 88: 481–488.
43. Willson J, Amliwala K, Harder A, Holden D L, Walker RJ. The effect of the anthelmintic emodepside at the neuromuscular junction of the parasitic nematode *Ascaris suum*. Parasitol 2003; 126:79–86.
44. Saeger B, Schmitt-Wrede HP, Dehnhardt M, Benten WP, Krucken J, Harder A, et al. Latrophilin-like receptor from the parasitic nematode *Haemonchus contortus* as target for the anthelmintic depsipeptide PF1022A. FASEB J 2001; 15:1332–1334.
45. Willson, J, Amliwala, K, Davis A, Cook A, Cuttle MF, Kriek N, Hopper NA, O'Connor V, Harder A, Walker RJ, Holden D L. Latrotoxin receptor signaling engages the UNC-13-dependent vesicle-priming pathway in *C. elegans*. Curr Biol 2004; 14: 1374–1379.
46. Guest M, Bull K, Walker RJ, Amliwala K, O'Connor V, Harder A, et al. The calcium-activated potassium channel is required for the action of the novel cyclo-octadepsipeptide anthelmintic, emodepside, in *Caenorhabditis elegans*. Int J Parasitol 2007; 37: 1577–1588.
47. Guest M, Bull K, Walker RJ, Amliwala K, O'Connor V, Harder A, et al. The calcium-activated potassium channel is required for the action of the novel cyclo-octadepsipeptide anthelmintic, emodepside in *Caenorhabditis elegans*. Int J Parasitol 2007; 37:1577–1588.
48. Gilles H M, Hoffman PS. Treatment of intestinal parasitic infections: a review of nitazoxanide. Trends Parasitol 2002; 18: 95–97.
49. Greenwood K, Williams T, Geary T. (2005). Nematode neuropeptide receptors and their development as anthelmintic screens. Parasitology 2005; 131: S169–S177.