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Review

Dynamics of some anthelmintic on internal parasites in camels: Review

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Abstract

In the current review, the focus will be applied to the mechanism of actions that are related to some anthelmintic medicines used for the treatment of gastrointestinal parasites of camels. This interesting subject is appealing because the importance of the host itself, camel, in providing relevant-region people in the world with milk, meat, and sometimes performance activities via camel races especially such races that are held in Arab Gulf region. The other aspect is that the huge economic and health losses that are generated by these infestation to camels. According to a study from Al-Diwaniyah City, Iraq, 86.36% of the tested camels were infested with different genera of GIT parasites such as Fasciola spp, Eimeria spp, Cryptosporidium spp, Nematodirus spp, Trichostrongylus spp, Moneizia spp, and Trichuris spp. In principle, some anthelmintic medicines generate undesired effects on the nematode-neuromuscular system. Some agents, such as benzimidazoles, bind to the β-tubulin in the parasite leading to microtubule-polymerization deactivation and finally death of the parasitic cells.

Keywords: Aanthelmintic agents, Camels, Dynamics**.**

Introduction

Camels, *Camelus dromedaries*, are considered important animals in the relevant regions of the world, they tolerate hot and tough climates such as dessert. Many countries in Arab and Africa regions rely on the consumption of camel-based products, they provide people with milk, meat, and hide-based materials used in the industries of clothing (1–5). About the geographical presence of these interesting animals, regions in Africa have the largest proportion, 85%, of camel population in the world, 25.89 million (7). Maintaining and growing up such populations of camels need to provide them with suitable management (8). However, these animals are affected by host-specific diseases caused by different infectious agents, and GIT parasites represent a significant part of these causative agents. Regarding these parasites, *Haemonchus*, *Nematodirella*, *Nematodirus*, *Trichostrogylus*, *Strogyloides*, *Ostertagia*, *Marshallagia*, *Cooper a*, *Trichuris*, *and Camelostrongylus* are considered as the major nematodes that induce these parasitic infections in the GITs of camels. Moreover, the increase of these infections are recorded in rainy periods more than that in summer (8). The clinical manifestation of these infections are characterized by the presence of loss of appetite, weight decrease, hair-coat disorders, anemia, edemas of limbs, and well-noticed pica (8). In Iraq, some GIT parasites that infect camels are *Fasciola* spp, *Eimeria* spp, *Cryptosporidium* spp, *Nematodirus* spp, *Trichostrongylus* spp, *Moneizia* spp, and *Trichuris* spp (9). Some agents, such as benzimidazoles, bind to the β-tubulin in the parasite leading to microtubule-polymerization deactivation and finally death of the parasitic cells (10). Controlling these infestations needs for researchers to understand the mechanisms of action of the treatment used for eliminating

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the causative agents (11). For this reason, the review here will focus on these mechanisms for certain anthelmintic agents used to control certain groups of GIT parasites.

1- Albendazole (ALB)

This agent belongs to the group of benzimidazoles. These are efficient agents in treating these parasitic infections, It has been approved that ALB binds strongly to the β-tubulin in the parasite leading to microtubule-polymerization deactivation and finally death of the parasitic cells (8-20). Older ideas were that this agent was effective agents certain enzymatic systems in the parasite cells (12–20). Figure, 1, shows the effect of ALB on the process of polymerization in the cells of parasites (22).

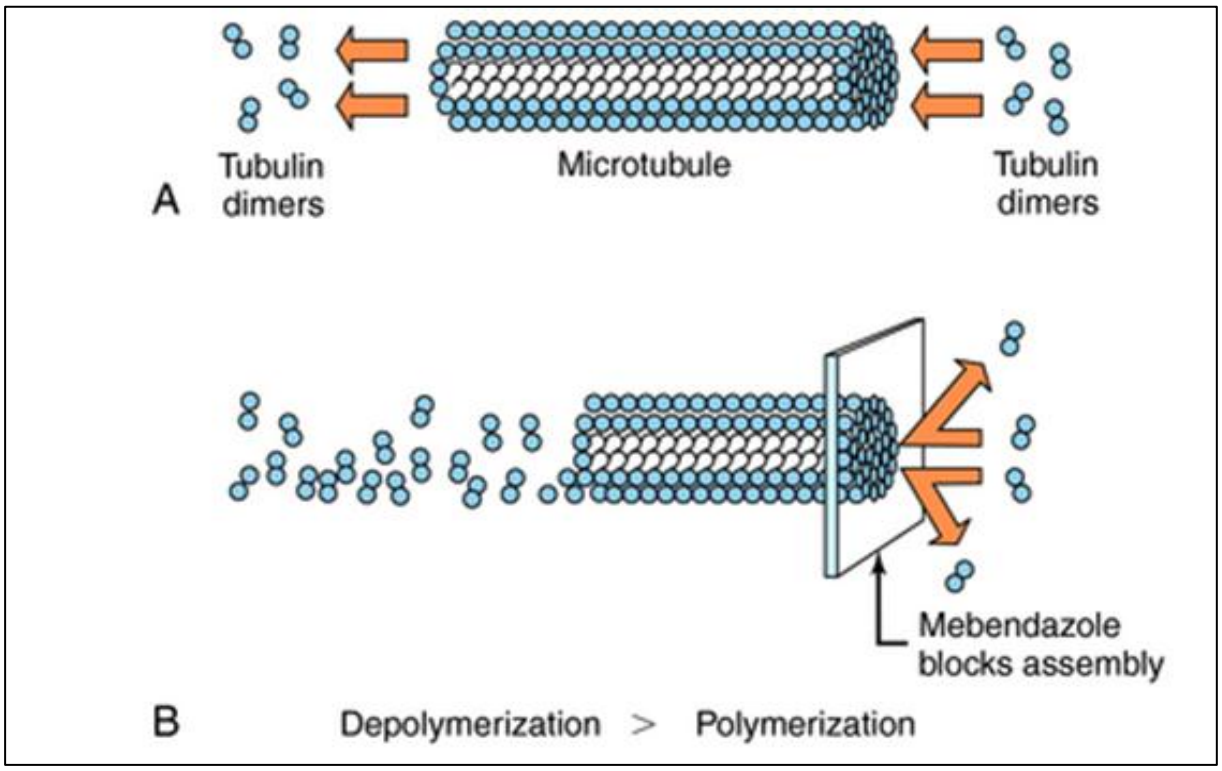

Figure (1): shows the depolymerization effect of the mebendazole or ALB in parasitic cells (22).

In case of resistance, it was found that changes in the genetic materials such as the presence of certain mutations such as those responsible of generating drug targets such as β-tubulin target leads to encouraging drug resistance against these compounds, in addition, different SNPs in this gene were found to be important in developing such resistance against benzimidazole compounds as shown to be increased after treatment (22,23). The transcription factor SKN-1 and detoxification gene *ugt-22* were found to alter albendazole-based efficacy in *Caenorhabditis elegans* indicating big roles for these materials in developing resistance in helminths via glucose conjugation of albendazole-related agents (24). These mechanisms involve three detoxification phases. In phase I, the medicine is converted to present hydrophilic groups anchoring phase II conjugation to water-soluble moieties such as glucose and glutathione. Then, pumping out of these conjugated metabolite is occurred by phase III transporter proteins, and the enzymes related to these phases are cytochrome P450s (CYPs) and short-chain dehydrogenases/ reductases for phase I, glutathione-S-transferases (GSTs) and UDP-glycosyltransferases (UGTs) for phase II, and efflux-pumping related ATP-binding cassette

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(ABC) transporters for Phase III (23), figure 2 (24).

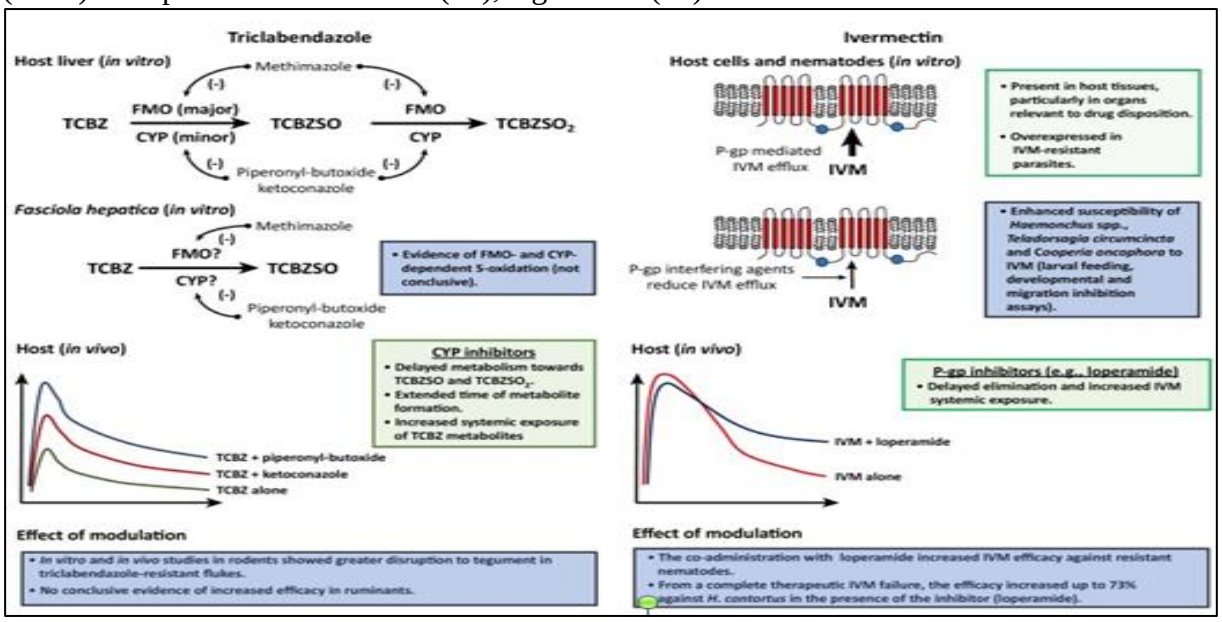

Figure (2): Enzymatic detoxification of anthelminthic drugs (24)

2- Macrocyclic lactones (MLs)

These are antiparasitic agents with broad-spectrum capabilities to fight nematodes. These include Ivermectins and milbemycins. Ivermectin is considered the available drug for commercial use (22-25). These agents are produced by *Streptomycetes*, bacteria from soil (25-28). The actions of these agents are represented by their selective agonists of glutamate-gated chloride channels (GluCls) of nematode-related nervous parts and muscles of the pharynx (25,26). This target is abscent in camels. GluCls activation will limit the pharyngeal pumping and mobility (28,29). Moreover, 4-aminobutyric acid (GABA) and nicotinic-based receptors will be deactivated leading to dysfunction of the nematode-based somatic muscles (30-35). Figure 2 reveals the mechanism of action of Ivermectin (36).

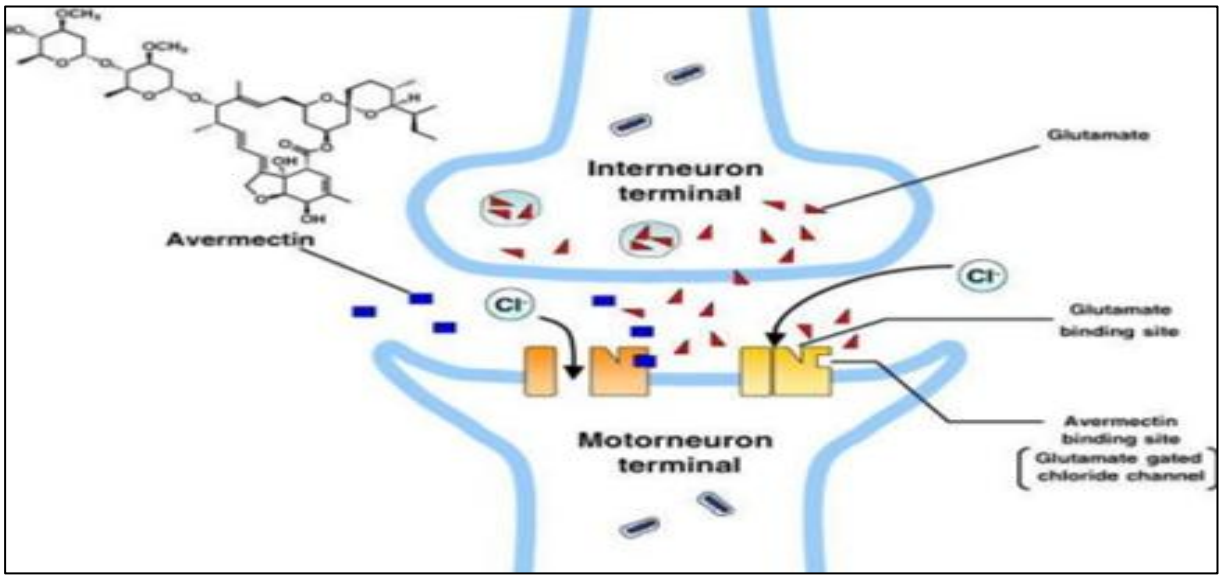

Figure (2): reveals the mechanism of action of Ivermectin (36).

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Interestingly, it was revealed that ivermectin and its targets share mechanisms of ion channels and receptors modulations, and it was found that the drug eliminate the worms by stimulating glutamate-gated Cl- channels, targeting several ligand-gated ion channels and receptors such as Cys-loop receptors, P2X4 receptors, and fernesoid X receptors in addition activating the G-protein-gated inwardly rectifying K+ channel (38).

3- Spiroindoles

These are anti-parasitic agents that work by deactivating the nAChRs generating flaccid paralysis in nematodes. Then, the paralyzed nematodes will be expulsed from the intestine of the host (35-36). This agent was reported to be used in sheep, but there are no reports for its use in camels as it is a newly made anti-parasitic agent (34-35). These medicines could be represented by Derquantel (2-deoxy-paraherquamide or PNU-141962) (38–40).

4- Imidazothiazoles

These antiparasitic agents cause spastic paralysis in parasites due its binding to nAChRs of the muscles that belong to the body wall of the parasite, tetramisole was the first generation of this group and was followed by the use of levamisole (37). Figure 3 identifies the mechanism of action of levamisole (41).

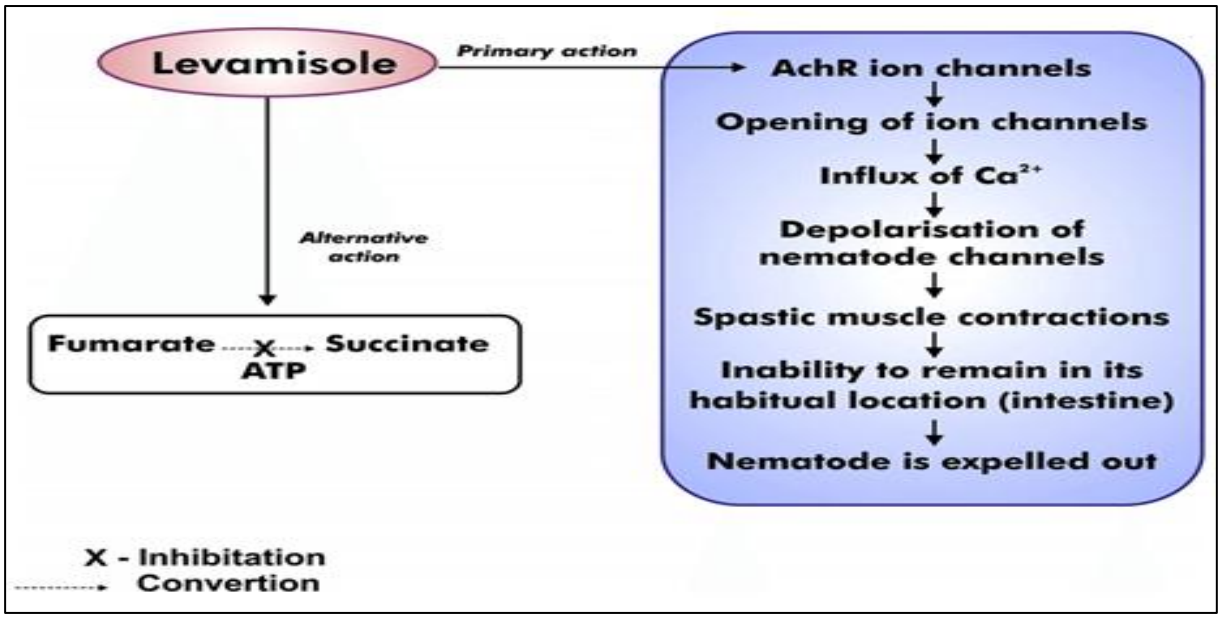

Figure 3: identifies the mechanism of action of levamisole (41).

Conclusion

This review reveals that the anti-parasitic drugs used for treatment of GIT parasites in camels have different mechanisms of action to work. The general mode is to deactivate certain abilities of the nervous system that belongs to the parasite leading to paralyze the parasite and to be expulsed later by the host.

References

1.Aboma R, Nesibu A, Birhanu H, Yisehak T, Teshale S. Internal and external parasites of camels (Camelusdromedarius) slaughtered at Addis Ababa Abattoir, Ethiopia. *J Vet Med Anim Heal.* 2015; 72:57-63.

2.Hirad AH, Ahmad J, Alkhedhairy AA, Bahkali AH, Khan ST. Bacterial isolates exhibiting multidrug resistance, hemolytic activity, and high 16S rRNA gene similarity with well-known pathogens found in camel milk samples of Riyadh region. APMIS. 2018; 1263:215-26.

3.Arab HH, Salama SA, Abdelghany TM, Omar HA, Arafa E-SA, Alrobaian MM. Camel Milk Attenuates Rheumatoid Arthritis Via Inhibition of

Al-Qadisiyah Journal of Veterinary Medicine Sciences
(P-ISSN 1818-5746/ E-ISSN 2313-4429)
www.qu.edu.iq/journalvm

Mitogen Activated Protein Kinase Pathway. Cell Physiol Biochem. 2017;432:540–52.
4. Al-Fatlawi MAA. The diagnosis of Echinococcus granulosus strain in sheep, cattle and camel in Al-Qadisya governemerate. *Al-Qadisiyah J. Vet. Med. Sci*. 2006; 5(2):53-60.
5. Al-Hindawe AJ. Seroprevalence of Toxoplasmosis Toxoplasma gondii infection in the camels in Al-Qadisiya province. *Al-Qadisiyah J. Vet. Med. Sci.* 2006; 5(2):71-73.
6. Al-Fatlawi MAA, Al-Shimary FJH. Effect of freezing on hatching period of Fasciola spp. eggs. *Al-Qadisiyah J. Vet. Med. Sci*. 2008; 7(1):44-47.
7. Demelash K, Alemu F, Niguse A, Feyera T. Prevalence of Gastrointestinal Parasites and Efficacy of Anthelmintics Against Nematodes in Camels in Yabello District, Southern Ethiopia. 2014;5(3):223-31.
8. Parsani HR, Singh V, Momin RR. Common parasitic diseases of camel. *Vet World*. 2008;1(10):317-8.
9. Karawan A chaffat. Diagnostic study of internal parasites in camels of Al- diwaniya government Lecturer Azhar chaffat karawan. *Kufa J Vet Med Sci*. 2017;8(1):64–71.
10. Robinson MW, McFerran N, Trudgett A, Hoey L, Fairweather I. A possible model of benzimidazole binding to β-tubulin disclosed by invoking an inter-domain movement. J Mol Graph Model. 2004;233:275-84.
11. Bansal Y, Silakari O. The therapeutic journey of benzimidazoles: A review. *Bioorg Med Chem*.2012; 20(21):6208-36.
12. Lacey E. Mode of action of benzimidazoles. Parasitol Today [Internet]. 1990; 64:112–5.
13. McKellar QA, Scott EW. The benzimidazole anthelmintic agents--a review. *J Vet Pharmacol Ther*. 1990;13(3):223-47.
14. Prichard RK. Mode of action of the anthelminthic thiabendazole in Haemonchus contortus. Nature. 1970;2285272:684–5.
15. Tejada P, Sanchez-Moreno M, Monteoliva M, Gomez-Banqueri H. Inhibition of malate dehydrogenase enzymes by benzimidazole anthelmintics. *Vet Parasitol.* 1987;243-4:269-74.
16. Salahuddin, Shaharyar M, Mazumder A. Benzimidazoles: A biologically active compounds. *Arab J Chem.* 2017;10:S157-73.
17. Ansari KF, Lal C. Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents. *Eur J Med Chem.* 2009; 44(5):2294-9.
18. Amari M, Fodili M, Nedjar-Kolli B, Hoffmann AP, PÉriÉ J. Reactivity studies on 4-aminopyrones: Access to benzimidazole and benzimidazolone derivatives. *J Heterocycl Chem*. 2002;394:811-6.
19. Demirayak Ş, Abu Mohsen U, Çağri Karaburun A. Synthesis and anticancer and anti-HIV testing of some pyrazino[1,2-a]benzimidazole derivatives. *Eur J Med Chem*. 2002; 37(3):255-60.
20. Evans D, Hicks T, Williamson W, Dawson W, Meacock S, Kitchen E. Synthesis of a group of 1H--benzimidazoles and their screening for antiinflammatory activity. *Eur J Med Chem.* 1996; 31(7)8:635-42.
21. http://www.plaridel.com.ph/blog/albendazole-safety.Albendazole Safety Plaridel Products and Services, Inc. [Internet]. 2018 [cited 2018 Dec 16]. Available from: http://www.plaridel.com.ph/blog/albendazole-safety
22. Diawara A, Halpenny CM, Churcher TS, Mwandawiro C, Kihara J, Kaplan RM, et al. Association between response to albendazole treatment and β-tubulin genotype frequencies in soil-transmitted helminths. *PLoS Negl Trop Dis*. 2013;75: 2247.
23. Fontaine P, Choe K. The transcription factor SKN-1 and detoxification gene ugt-22 alter albendazole efficacy in Caenorhabditis elegans. *Int J Parasitol Drugs drug Resist*. 2018; 82:312–9.
24. Lanusse C, Canton C, Virkel G, Alvarez L, Costa-Junior L, Lifschitz A. Strategies to Optimize the Efficacy of Anthelmintic Drugs in Ruminants. *Trends Parasitol.* 2018; 34(8):664–82.
25. Zhuo Y, Zhang T, Wang Q, Cruz-Morales P, Zhang B, Liu M, et al. Synthetic biology of avermectin for production improvement and structure diversification. *Biotechnol J.* 2014; 9(3):316–25.
26. Merola VM, Eubig PA. Toxicology of avermectins and milbemycins macrocylic lactones and the role of P-glycoprotein in dogs and cats. *Vet Clin North Am Small Anim Pract.* 2012; 42(2):313-333.
27. Wolstenholme AJ, Rogers AT. Glutamate-gated chloride channels and the mode of action of the avermectin/milbemycin anthelmintics. Parasitology. 2006; 131S1:S85.
28. Abongwa M, Buxton SK, Robertson AP, Martin RJ. Curiouser and Curiouser: The Macrocyclic Lactone, Abamectin, Is also a Potent Inhibitor of Pyrantel/Tribendimidine Nicotinic Acetylcholine Receptors of Gastro-Intestinal Worms. Aroian R V., editor. *PLoS One.* 2016; 11(1):e0146854.
29. Holden-Dye L, Walker RJ. Avermectin and avermectin derivatives are antagonists at the 4-aminobutyric acid GABA receptor on the somatic muscle cells of Ascaris; is this the site of anthelmintic action? *Parasitology*. 1990;101 Pt 2:265-71.
30. Puttachary S, Trailovic SM, Robertson AP, Thompson DP, Woods DJ, Martin RJ. Derquantel and abamectin: effects and interactions on isolated tissues of Ascaris suum. *Mol Biochem Parasitol.* 2013;1882:79-86.
31. Nolan TJ, Lok JB. Macrocyclic lactones in the

Al-Qadisiyah Journal of Veterinary Medicine Sciences
(P-ISSN 1818-5746/ E-ISSN 2313-4429)
www.qu.edu.iq/journalvm

treatment and control of parasitism in small companion animals. *Curr Pharm Biotechnol*. 2012; 13(6):1078-94.

32. Martin RJ, Robertson AP, Wolstenholme AJ. Mode of action of the macrocyclic lactones. In: Macrocyclic lactones in antiparasitic therapy. Wallingford: CABI; 2018; p. 125-40.
33. Nra. NRA Special Review of MACROCYCLIC LACTONES. 1998; Available from: https://apvma.gov.au/sites/default/files/publication/14406-macrocyclic-lactones-review-report_.pdf
34. Organization WH. Ivermectin for malaria transmission control. 2016; Available from: https://www.who.int/malaria/mpac/mpac-sept2016-invermectin-presentation.pdf
35. Chen I-S, Kubo Y. Ivermectin and its target molecules: shared and unique modulation mechanisms of ion channels and receptors by ivermectin. *J Physiol.* 2018; 59610:1833–45.
36. Chandy ML, Soman C, Kumar SP, Kurup S, Jose R. Understanding molecular mechanisms in multivariant actions of levamisole as an anti-helminthic, anti-inflammatory, antioxidant, anti-neoplastic and immunomodulatory drug. J Oral Maxillofac Surgery, *Med Pathol.* 2016; 284:354-7.
37. Chen I-S, Kubo Y. Ivermectin and its target molecules: shared and unique modulation mechanisms of ion channels and receptors by ivermectin. *J Physiol.* 2018; 59610:1833-45.
38. Little PR, Hodge A, Maeder SJ, Wirtherle NC, Nicholas DR, Cox GG, et al. Efficacy of a combined oral formulation of derquantel–abamectin against the adult and larval stages of nematodes in sheep, including anthelmintic-resistant strains. *Vet Parasitol*. 2011; 1812-4:180-93.
39. Rufener L, Baur R, Kaminsky R, Mäser P, Sigel E. Monepantel allosterically activates DEG-3/DES-2 channels of the gastrointestinal nematode Haemonchus contortus. *Mol Pharmacol*. 2010; 785: 895-902.
40. Robertson AP, Clark CL, Burns TA, Thompson DP, Geary TG, Trailovic SM, et al. Paraherquamide and 2-deoxy-paraherquamide distinguish cholinergic receptor subtypes in Ascaris muscle. *J Pharmacol Exp Ther*. 2002; 3023:853-60.
41. Chandy ML, Soman C, Kumar SP, Kurup S, Jose R. Understanding molecular mechanisms in multivariant actions of levamisole as an anti-helminthic, anti-inflammatory, antioxidant, anti-neoplastic and immunomodulatory drug. *J Oral Maxillofac Surgery, Med Pathol*. 2016; 284:354-7.