

Review Article:

Ivermectin: An Effective Remedy Against Various Diseases: A Literature Review



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Cite this article as: Gholami MH, Hashemi F, Entezari M. Ivermectin: An Effective Remedy Against Various Diseases: A Literature Review. Archives of Advances in Biosciences. 2022; 13:E35552. <https://doi.org/10.22037/aab.v13i.35552>

<https://doi.org/10.22037/aab.v13i.35552>



Article info:

Received: 07 Aug 2021

Accepted: 27 Aug 2021

Published: 01 Feb 2022

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Abstract

Introduction: Ivermectin is a member of avermectins family which was discovered in 1967 in Japan. The contribution of this drug to animal and human health was so prominent that the researchers who found the drug were awarded a Noble prize in 2015. With the advent of COVID-19, lot of interest has shifted more towards ivermectin usage in treating the COVID-19 alone or in combination with other medicines as synergism. Since its introduction, ivermectin has helped to control many parasitic diseases of animals and humans. For many years after its discovery, ivermectin was considered to be only a parasitic agent, but as scientists continue to evaluate this drug, they discover more healing aspects.

Materials and Methods: For this review, we searched keywords from international databases including PubMed, Google Scholar, Science Direct and Scopus. The keywords were ivermectin, anticancer, anti-inflammation, antibacterial, antiviral, antiparasitic, and mechanism of action.

Results: Several studies have shown that ivermectin has a very powerful antiparasitic, antibacterial, and antiviral activity and it can also be used as an anticancer and anti-inflammatory agent.

Conclusion: The collected data showed that ivermectin can be used to control and prevent many pathogenic agents and it can also be repurposed for the treatment of COVID-19.

Keywords: Ivermectin, Antiparasitic agent, Immunity, Anticancer agent

1. Introduction

The antiparasitic drug ivermectin was discovered in 1967 in the Japanese Kitasato Institute [1] in fermentation broths of actinomyces cultures with the fungus streptomyces avermitilis [2-4]. Ivermectin is a member of Avermectins class (AVM), which consists of 16-macrocyclic lactone compounds [5-7], including

moxidectin, abamectin and selamectin among other subgroup members [7]. The initial approval of the drug for animal use was in 1981 [8, 9]. Later in 1987, it was also approved by Food and drug administration (FDA) for use in humans for oral treatment of onchocerciasis (river blindness) caused by parasite *Onchocerca volvulus* and transmitted by blackfly among human population mostly in West and Central Africa [5, 6]. It is very efficient in eliminating the parasites of GI tract and fi-

larial infections [10]. Since its use in human medicine, the lives of billions of people around the world have improved because of this drug. Furthermore, it has been used in veterinary medicine to treat billions of pets and livestock, boosting the food and leather production as well as improving the well-being of pets worldwide [1]. Ivermectin has sold more than 1 billion United States Dollar (USD) per annum over the last 20 years [7] and around 250 million people are using the drug annually [5]. In the AVM class, ivermectin is the most used drug, being a safer and more potent combination of two AVMs 22,23-dihydroavermectin-B1a and dihydroavermectin-B1b, at 4:1 ratio, respectively [5]. Its use is not restricted to one specific area; it has been also utilized for aqua- and agricultural purposes, but it is mainly known as an antiparasitic and insecticidal agent [2-4, 7, 11]. Figure 1 represents the chemical structure of the most popular AVM members. In 2015, William C. Campbell and Satoshi Omura, who discovered and developed the drug, received the Nobel Prize in Physiology or Medicine for their prominent work and the impact it had on global health, economy and welfare [8, 9, 12].

Ivermectin has an extraordinary advantage – there has not been a single report on parasites that have elevated resistance to drugs, even those in human populations receiving ivermectin as a monotherapy for more than 30 years [13]. Also, this ‘wonder’ drug has a very wide safety margin in equine, pigs, ruminants and most breeds of dogs [14, 15]. Its acute toxicity has been studied in many animals and signs of toxicity were similar on either Per os (PO) or Intraperitoneal (IP) route, which included ataxia, reduced activity, and tremor [16]. Due to confinement of ivermectin targets within Central nervous system (CNS), the toxicity in human population is very low [1]. The side effects are only those caused by inflammatory and immune responses against the parasite, e.g. fever, skin rashes, malaise and pruritis [11, 17], which occur within 24-48 h post-treatment [18].

Nowadays, drug repurposing and repositioning have made this drug relatively unknown as new use of ivermectin has been successfully applied to prevent and treat a wider extent of diseases [19]. Examples of such diseases are trichinosis [20], malaria [21], orbital myiasis [22], leishmaniasis [23], asthma [24], epilepsy [25], African trypanosomiasis [26], neurological diseases [5], anti-

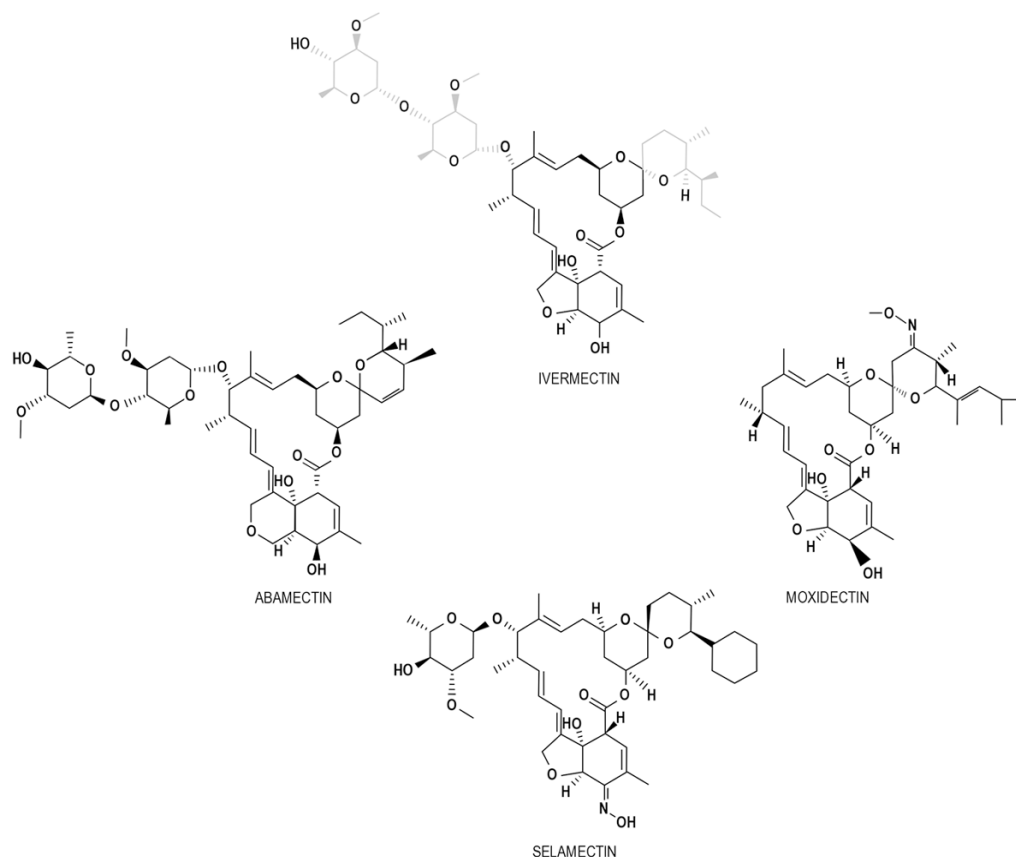


Figure 1. Most popular compounds of the AVM class. Note that all of them have bisoleandroxy substituent at C13 with 16-carbon macrocyclic lactone core. IUPAC name of ivermectin is 22,23-dihydroavermectin B1a + 22,23-dihydroavermectin B1b.

ral activities [27] (e.g. HIV¹, dengue, encephalitis [28]), antibacterial effects (tuberculosis and Buruli ulcer [29]), anticancer (cervical cancer, glioblastoma, gastric cancer, leukemia, breast cancer, ovarian cancer, colon cancer, melanoma, and lung cancer [5]). This versatile nature of ivermectin raises the possibility of becoming an even more outstanding drug in the future. In the current study, we covered all features and potentials of ivermectin and its broad spectrum of efficiency among different species, pathogens or even diseases.

Mechanism of action

Several mechanisms of actions have been described for ivermectin. Most known and recognized mechanism of ivermectin is to enhance the activity of glutamate-gated chloride ion channels or Gamma-aminobutyric acid (GABA) receptors in helminths and parasites [30]. In mammals, GABA sensitive neurons are within CNS and BBB (Blood Brain Barrier) which protect vertebrates from potential negative effects of ivermectin [10]. However, the dose-dependent susceptibility of invertebrates to ivermectin is due to the vast distribution of Cl⁻ channels, where ivermectin can generate an influx of chloride ion and cause hyperpolarization leading to hampering the phosphorylation of myosin II light chain [10]. This event results in somatic muscle paralysis alongside consequent unsteady movement, starvation, and death. Starvation results from the inhibition of pharyngeal pumping. The affinity of ivermectin for parasite is 100 times more than for brain of vertebrates [1]. Another mechanism that ivermectin exerts its effect is by immunomodulation, which is by activating neutrophils,

1. Human Immunodeficiency Virus

increasing C-reactive protein and Interleukin-6 (IL-6) levels [31]. Ivermectin believed to exert its antiviral efficacy by inhibiting the nuclear import of proteins of virus and host. At the time of infection, almost all RNA viruses are IMP α / β 1-dependent and ivermectin hampers the import of this viral interface, thereby boosting antiviral response [32]. Another mechanism is believed to be through CD147 transmembrane receptor. ACE-2 and CD147 are known as key binding site for spike protein of SARS-COV-2 [33]. Moreover, a possible ionophore role has been speculated by Rizzo. Ionophores are mostly known for their antibiotic activity; Besides, antiviral and anticancer activities are also suggested [34].

Ivermectin can exert its effects through another mechanism that involves the allosteric modulation of the P2X₄ receptor. P2X receptors are ATP-gated channels which are selective for cations [35]. They moderate several functions via extracellular ATP [36]. P2X₄, of 7 subunits of P2X receptors, has the most sensitivity to ivermectin. Priel et al. observed mix patterns and relations between ivermectin concentration and potency of ATP, so they concluded that probably ivermectin binds to various sites with different affinities [35]. Figure 2 is a graphical abstract of the potential mechanisms of ivermectin.

Antiparasitic

Most known use of this drug is for its antiparasitic effects and there has been numerous confirming studies. Surgical removal of fly larvae is the only treatment to myiasis but it is not available to many people in poor countries. Ivermectin has been successfully used as a non-invasive method for the treatment of oral myiasis

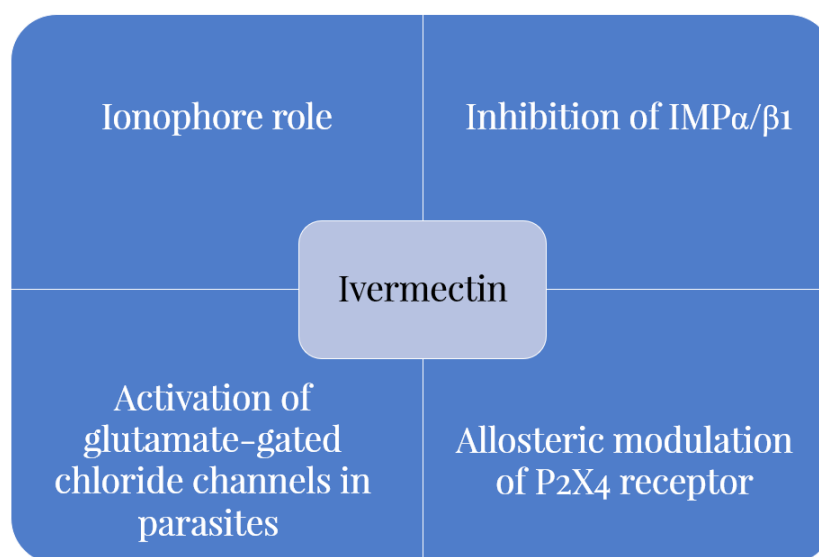


Figure 2. Proposed mechanisms of ivermectin

[37] and also orbital myiasis [38]. Trichinosis is a prevalent roundworm infection, i.e., 11 million infected individuals, and ivermectin can eliminate *Trichinella spiralis*, the responsible roundworm [39].

Ivermectin can also kill *Anopheles gambiae*, the mosquito transmitting the parasite of malaria, if the drug has been delivered to human body via proper oral dose [40-43]. Also, it has been demonstrated by micromolecular implements that ivermectin can destroy the *Plasmodium falciparum*, malaria-causing parasite, via inhibiting the nuclear import of Polypeptides of its Signal Recognition Particle (PfSRP). Therefore, combining ivermectin with other anti-malarial drugs could become a powerful tool for controlling malaria [44, 45].

It has also been suggested as an insecticide to control Phlebotomine sandfly vectors which transmit *Leishmania parasites* [23, 46]. Ivermectin had positive effects against *Phlebotomus papatasi* and *Leishmania major* promastigotes and showed to be more effective in eliminating promastigotes than erythromycin, rifampicin, and nystatin [47, 48]. Also, in an *in vitro* study, ivermectin was more efficient than other drugs used for cutaneous leishmaniasis in eliminating *Leishmania tropica* [44]. In combination with surgical wound dressing, ivermectin holds great promise to cure cutaneous leishmaniasis [49].

Sleeping sickness (African trypanosomiasis) has been another victim of ivermectin's killings due to the fact that if tsetse flies (*Glossina palpalis*) consume the blood of animals treated with ivermectin, they die within 5 days and this has showed promising future for the control of sleeping sickness [50, 51]. Moreover, in another study, ivermectin doubled the survival time for the mice infected with *Trypanosoma brucei*, suggesting that the use of ivermectin can be assessed from different aspects in the treatment of African trypanosomiasis [26]. The use of ivermectin for dogs suffering from *Trypanosoma cruzi* (American trypanosomiasis; AKA Chagas disease) has been successfully exterminated the ticks with no effect on host or infection [52].

More than 200 million individuals around the world suffer from schistosomiasis disease caused by *Schistosoma* species. Praziquantel is the choice drug for preventing and treating the disease but resistant parasites are becoming a worrisome problem [53, 54]. Glutamate signaling is recorded in schistosomes; since ivermectin is a powerful agonist of glutamate-gated chloride channels, it is possible to use ivermectin to cure this disease [55, 56]. Researchers in Egypt evaluated the effect of ivermectin

on mice infected with *Schistosoma mansoni*. They concluded that ivermectin can eliminate the parasite due to its schistosomocidal effects on adult worm, especially females, and ovicidal effects, as well as treating hepatic lesions [57, 58]. Interestingly, ivermectin has been reported to eliminate *Biomphalaria glabrata*, intermediate snail involved in schistosomiasis re-infection cycle; this holds a promise that ivermectin can help us to control this neglected major tropical disease [59, 60].

Cimex lectularius, common bedbug, feeds solely on human blood and has been a major issue in poor households of Europe and North America. Sheele et al., in 2013 showed that ivermectin is very effective against bedbugs; this could prevent and also eradicate the infestations of bedbugs [61].

Antiviral

Antiviral activity of ivermectin is vastly studied. Since the recent COVID-19 outbreak, the study of ivermectin has increased drastically. In an *in vitro* study by Caly et al., Vero/hSLAM cells infected with COVID-19 virus was treated with ivermectin and 5000-fold reduction was reported within 48 hours, i.e., eliminating almost all virus particles [62]. Also, Ahmed et al., in 2021 showed that 5-day course with ivermectin treatment can reduce the duration of illness for COVID-19 virus [63]. Also, lower incidence of COVID-19 has been reported with prophylactic administration of ivermectin [64]. Moreover, ivermectin has been found to be safe in patients with acute myelogenous leukemia [65]. Popp et al., reported that ivermectin does not possess any proven efficacy against COVID-19 [66].

Ivermectin was tested in an *in vitro* study on Huh-7 cells infected with Zika Virus (ZIKV) and its antiviral effect was confirmed [67]. However, in Ketkar et al.'s study in 2019 on Ifnar1 knockout mice, no prophylactic effect was found after 4 mg kg⁻¹ IP injection on ivermectin. Also, no difference in mortality or morbidity was found. Authors speculated that the ineffectiveness is due to a low-dose administration of ivermectin and suggested that more investigations be done to evaluate the effect of ivermectin on ZIKV [68].

Study on different types of cell lines infected with ZIKV strain MR766 in an *in vivo* study that received 20 µM ivermectin 12 h Post Infection (HPI) demonstrated the antiviral effects of ivermectin. NS5² is needed for the replication of RNA viruses and the study showed that ivermectin inhibits the nuclear import of NS5 effectively

2. Nonstructural protein 5

[69]; this was compatible with previous studies [70, 71] which showed that ivermectin inhibits Dengue Virus (DENV) proliferation by the same mechanism. The effect of nanoparticle ivermectin (T-Fc-IVM-NP) was evaluated on Zika virus in a recently published *in vivo* and *in vitro* study. In this research, which used Caco-2 (human epithelial colorectal adenocarcinoma cells) and Balb/c albino mice, the expression of NS1 was suppressed by nanoparticle ivermectin, showing that it can be a safe agent to control ZIKV [72].

Dengue Virus (DENV) is an RNA virus belonging to genus flavivirus in Flaviviridae family. In an *in vitro* study on HeLa cells (human cervical adenocarcinoma), it was demonstrated that high doses of ivermectin (25–50 μM) can inhibit the proliferation of DENV [71]. In another *in vitro* study, ivermectin was found to have inhibitory effects against DENV, Yellow Fever Virus (YFV) and West Nile Virus (WNV), in which ivermectin showed a more powerful inhibitory effect against YFV compared to DENV and WNV. Authors claimed that ivermectin exerted its effects via the inhibition of the NS3 helicase domain and did not have any effects on the activity of ATPase. They also concluded that ivermectin can be used to prevent or treat the early stages of viral infections rather than advanced forms [73]. Yang et al., infected Vero cells with DENV2 and treated with ivermectin. The results indicated the EC₅₀ of ivermectin to be 0.5 μM , proving it as a strong inhibitor of DENV2 [28].

Avian Influenza (AI) is a negative-sense, single-stranded RNA virus, which belongs to Orthomyxoviridae family. Gotz et al. [74] studied the effect of ivermectin on chicken hepatocellular carcinoma cells infected with AI type A and showed that nuclear transmission of various viral ribonucleoprotein complexes can be prevented at 10 μM ivermectin.

HIV-1 is an RNA virus belonging to the genus Lentivirus and family of Retroviridae. Wagstaff et al. designed an *in vitro* study and assessed the effect of ivermectin on the nuclear transfer of HIV-1. They found that ivermectin can reduce the binding of NLS-containing protein via IMP α/β inhibition with IC₅₀ of 4.8 μM [75].

Newcastle Virus (NDV) is a single-stranded RNA virus belonging to paramyxoviridae family. In an *in vitro* and *in vivo* study, different doses of ivermectin were tested on chick primary fibroblast cell line and 9-day-old embryo. Authors found that doses higher than 100 $\mu\text{g/ml}$ have cytotoxic effects. Nevertheless, the safe concentration of ivermectin was at 50 $\mu\text{g/ml}$ or

less; there were no cytotoxic effects and antiviral activity was moderate to poor [76].

Antibacterial

The antibacterial properties of ivermectin have been recently discovered on which few studies are available. In an *in vitro* study by Ashraf et al., ivermectin showed inhibitory effects against certain isolates of *S. aureus* (i.e., 2 isolates among 21 tested isolates). Authors also mentioned that more studies are needed to comprehend the reason why ivermectin did not prevent all need of *S. aureus* [76]. Tan et al., developed a novel ivermectin, D4, and compared it with original ivermectin, D, in treatment of MRSA and its biofilm infections. The results showed that D4 is more powerful than D, with MIC of D4 and D to be 4 $\mu\text{g ml}^{-1}$ and 20 $\mu\text{g ml}^{-1}$, respectively. Also, the study of mechanism showed that D4 is stronger in eliminating cell wall of bacteria, permeating cell membrane and binding to the DNA of MRSA [78].

Anticancer

Before explaining the anticancer effects of ivermectin, it is better to review a number of key pathways in the cancer development. First of all, the Wnt signaling pathway is a very old and evolutionarily conserved pathway that play crucial roles in aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development. The Wnts are secreted glycoproteins and encompass a large family of nineteen proteins in humans hinting to a daunting complexity of signaling regulation, function and biological output. Wnt signaling regulates pattern formation during embryogenesis [79]. P21-activated kinase 1 (Pak1) is a member of the highly conserved family of serine/threonine protein kinases regulated by Ras-related small G-proteins, Cdc42/Rac1. Its roles has been demonstrated in cardiac diseases including disrupted Ca²⁺ homeostasis-related cardiac arrhythmias, adrenergic stress- and pressure overload-induced hypertrophy, and ischaemia/reperfusion injury [80]. The Hippo/YAP-Associated Protein (YAP) signaling pathway is a cell survival and proliferation control system with its main activity of regulating cell growth and organ volume. YAP operates as a transcriptional coactivator in regulating the onset, progression, and treatment response in numerous human tumors [81].

In the study of Dou et al., it was reported that ivermectin uses Akt/mTOR pathway for the induction of autophagy to reduce the multiplication of several breast cancer cell lines including MCF-7, MCF-10, and MDA-

MB-231. Ivermectin targeted P-21-Activated Kinase 1 (PAK1) for this purpose [82]. Moreover, in the study of Diao et al., in 2019, ivermectin inhibited the proliferation of the CMT7364 and CIPp canine breast tumor cell lines by cell cycle blockage without incrementing cell death. Authors speculate the mechanism to be via Wnt pathway inhibition [83].

In an *in vivo* and *in vitro* study by Nambara et al., ivermectin had inhibitory effects on the proliferation of gastric cancer cells, which was dependent on YAP1 (Yes-Associated Protein 1) [84]. Also, in Melotti et al., study in 2014 ivermectin prevented the multiplication of various cancers, including CC14, CC36, DLD1, and Ls174T colorectal cancer cell lines, as well as promoting apoptosis via Wnt pathway blockage [85]. In Nishio et al., study in 2016 on Mobla/lb-deficient mice, ivermectin prevented the development of hepatocellular carcinoma, which is the 4th leading cause of death by cancer around the world, by blocking the activity of YAP1 [86].

Studies have demonstrated that ivermectin can prevent the multiplication of five carcinomas of renal cells and they speculated the mechanism to be via the induction of mitochondrial dysfunction [87]. Nappi et al., in 2020 concluded that ivermectin had synergistic effect on increasing the activity of enzalutamide, an anti-androgen drug, in the LNCaP prostate cancer cell line [88]. Also, Sharmeen et al. showed that ivermectin has a positive preventive effect on DU145 prostate cancer cell line [89].

In Zhang et al., study in 2019, after the treatment with ivermectin, the cellular cycle of HeLa cell line was stopped at G1/S phase showing distinct morphological changes of apoptosis [90]. In Gallardo et al., study in 2016, melanoma carcinoma cells were treated with ivermectin and effectively inhibited the activity of melanoma [91].

2. Conclusion

Ivermectin was used as an antiparasitic agent upon discovery, but the present status of the drug is vague due to its huge effects on very wide range of diseases and pathogens. To the best of our knowledge, ivermectin can be used to treat and control viruses, bacteria, parasites, and cancer. Ivermectin provides new promising opportunities to control and prevent a completely new range of diseases, thus generating global interest in evaluating and conducting researches on this wonder drug. Further studies are needed to introduce new targets and mechanism of the disease; thus the effects of this marvelous medicine may gain more prominence.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Author's contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

This article was supported by Islamic Azad University, Tehran Medical Sciences Branch.

References

- [1] Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A. The multitargeted drug ivermectin: From an antiparasitic agent to a repositioned cancer drug. *Am J Cancer Res.* 2018; 8(2):317-31. [PMID] [PMCID]
- [2] Zhang Y, Luo M, Xu W, Yang M, Wang B, Gao J, et al. Avermectin confers its cytotoxic effects by inducing DNA damage and mitochondria-associated apoptosis. *J Agric Food Chem.* 2016; 64(36):6895-902. [DOI:10.1021/acs.jafc.6b02812] [PMID]
- [3] Albérich M, Ménez C, Sutra JF, Lespine A. Ivermectin exposure leads to up-regulation of detoxification genes in vitro and in vivo in mice. *Eur J Pharmacol.* 2014; 740:428-35. [DOI:10.1016/j.ejphar.2014.06.052] [PMID]
- [4] Zhang Y, Wu J, Xu W, Gao J, Cao H, Yang M, et al. Cytotoxic effects of avermectin on human HepG2 cells in vitro bioassays. *Environ Pollut.* 2017; 220(Pt B):1127-37. [DOI:10.1016/j.envpol.2016.11.022] [PMID]
- [5] Crump A. Ivermectin: Enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. *J Antibiot.* 2017; 70(5):495-505. [DOI:10.1038/ja.2017.11] [PMID]
- [6] Gloeckner Ch, Garner AL, Mersha F, Oksov Y, Tricoche N, Eubanks LM, et al. Repositioning of an existing drug for the neglected tropical disease onchocerciasis. *Proc Natl Acad Sci U S A.* 2010; 107(8):3424-9. [DOI:10.1073/pnas.0915125107] [PMID] [PMCID]
- [7] Hosseini Bai Sh, Ogbourne S. Eco-toxicological effects of the avermectin family with a focus on abamectin and ivermectin.

- tin. *Chemosphere*. 2016; 154:204-14. [DOI:10.1016/j.chemosphere.2016.03.113] [PMID]
- [8] Kircik LH, Del Rosso JQ, Layton AM, Schaubert J. Over 25 years of clinical experience with ivermectin: An overview of safety for an increasing number of indications. *J Drugs Dermatol*. 2016; 15(3):325-32. [PMID]
- [9] Canga AG, Prieto AMS, Liébana MJD, Martínez NF, Vega MS, Vieitez JJG. The pharmacokinetics and interactions of ivermectin in humans — A mini-review. *AAPS J*. 2008; 10(1):42-6. [DOI:10.1208/s12248-007-9000-9] [PMID] [PMCID]
- [10] Kaur H, Shekhar N, Sharma S, Sarma Ph, Prakash A, Medhi B. Ivermectin as a potential drug for treatment of COVID-19: An in-syn review with clinical and computational attributes. *Pharmacol Rep*. 2021; 73(3):736-49. [DOI:10.1007/s43440-020-00195-y] [PMID] [PMCID]
- [11] Ottesen EA, Campbell WC. Ivermectin in human medicine. *J Antimicrob Chemother*. 1994; 34(2):195-203. [DOI:10.1093/jac/34.2.195] [PMID]
- [12] Crump A, Omura S. Ivermectin, 'wonder drug' from Japan: The human use perspective. *Proc Jpn Acad Ser B*. 2011; 87(2):13-28. [DOI:10.2183/pjab.87.13] [PMID] [PMCID]
- [13] van Wyk JA, Malan FS, Randles JL. How long before resistance makes it impossible to control some field strains of *Haemonchus contortus* in South Africa with any of the modern anthelmintics? *Vet Parasitol*. 1997; 70(1-3):111-22. [DOI:10.1016/S0304-4017(96)01147-8]
- [14] McKellar QA, Benchaoui HA. Avermectins and milbemycins. *J Vet Pharmacol Ther*. 1996; 19(5):331-51. [DOI:10.1111/j.1365-2885.1996.tb00062.x] [PMID]
- [15] Burkhart CN. Ivermectin: An assessment of its pharmacology, microbiology and safety. *Vet Hum Toxicol*. 2000; 42(1):30-5. [PMID]
- [16] Umbenhauer DR, Lankas GR, Pippert TR, Wise LD, Cartwright ME, Hall SJ, et al. Identification of a P-glycoprotein-deficient subpopulation in the CF-1 mouse strain using a restriction fragment length polymorphism. *Toxicol Appl Pharmacol*. 1997; 146(1):88-94. [DOI:10.1006/taap.1997.8225] [PMID]
- [17] Dourmishev AL, Dourmishev LA, Schwartz RA. Ivermectin: Pharmacology and application in dermatology. *Int J Dermatol*. 2005; 44(12):981-8. [DOI:10.1111/j.1365-4632.2004.02253.x] [PMID]
- [18] De Sole G, Awadzi K, Remme J, Dadzie KY, Ba O, Giese J, et al. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. II. Adverse reactions. *Trop Med Parasitol*. 1989; 40(3):375-82. [PMID]
- [19] Ashour DS. Ivermectin: From theory to clinical application. *Int J Antimicrob Agents*. 2019; 54(2):134-42. [DOI:10.1016/j.ijantimicag.2019.05.003] [PMID]
- [20] El-Azzouni MZ. Effect of ivermectin on experimental trichinosis. *J Egypt Soc Parasitol*. 1997; 27(2):331-40. [PMID]
- [21] Ômura S, Crump A. Ivermectin and malaria control. *Malar J*. 2017; 16:172. [DOI:10.1186/s12936-017-1825-9] [PMID] [PMCID]
- [22] Osorio J, Moncada L, Molano A, Valderrama S, Gualtero S, Franco-Paredes C. Role of ivermectin in the treatment of severe orbital myiasis due to *Cochliomyia hominivorax*. *Clin Infect Dis*. 2006; 43(6):e57-9. [DOI:10.1086/507038] [PMID]
- [23] Kadir MA, Aswad HS, Al-Samarai AM, Al-Mula GA. Comparison between the efficacy of ivermectin and other drugs in treatment of cutaneous leishmaniasis. *Iraqi J Vet Sci*. 2009; 23(Suppl II):175-80. <https://www.researchgate.net/publication/237481636>
- [24] Alsharif A, Sodhi A, Murillo LC, Headley AS, Kadaria D. Wait!!! no steroids for this asthma.... *Am J Case Rep*. 2015; 16:398-400. [DOI:10.12659/AJCR.893729] [PMID] [PMCID]
- [25] Colebunders R, Mandro M, Mukendi D, Dolo H, Suykerbuyk P, Van Oijen M. Ivermectin treatment in patients with onchocerciasis-associated epilepsy: Protocol of a randomized clinical trial. *JMIR Res Protoc*. 2017; 6(8):e137. [DOI:10.2196/resprot.7186] [PMID] [PMCID]
- [26] Udensi UK, Fagbenro-Beyioku AF. Effect of ivermectin on *Trypanosoma brucei brucei* in experimentally infected mice. *J Vector Borne Dis*. 2012; 49(3):143-50. [PMID]
- [27] Heidary F, Gharebaghi R. Ivermectin: A systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot*. 2020; 73(9):593-602. [DOI:10.1038/s41429-020-0336-z] [PMID] [PMCID]
- [28] Yang SNY, Atkinson SC, Wang Ch, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin $\alpha/\beta 1$ heterodimer. *Antiviral Res*. 2020; 177:104760. [DOI:10.1016/j.antiviral.2020.104760] [PMID]
- [29] Csóka B, Németh ZH, Szabó I, Davies DL, Varga ZV, Pálóczi J, et al. Macrophage P2X4 receptors augment bacterial killing and protect against sepsis. *JCI Insight*. 2018; 3(11):e99431. [DOI:10.1172/jci.insight.99431] [PMID] [PMCID]
- [30] Kane NS, Hirschberg B, Qian S, Hunt D, Thomas B, Brochu R, et al. Drug-resistant *Drosophila* indicate glutamate-gated chloride channels are targets for the antiparasitics nodulisporic acid and ivermectin. *Proc Natl Acad Sci U S A*. 2000; 97(25):13949-54. [DOI:10.1073/pnas.240464697] [PMID] [PMCID]
- [31] Njoo FL, Hack CE, Oosting J, Luyendijk L, Stijlma JS, Kijlstra A. C-reactive protein and interleukin-6 are elevated in onchocerciasis patients after ivermectin treatment. *J Infect Dis*. 1994; 170(3):663-8. [DOI:10.1093/infdis/170.3.663] [PMID]
- [32] Choudhary R, Sharma AK. Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: Trends, scope and relevance. *New Microbes New Infect*. 2020; 35:100684. [DOI:10.1016/j.nmni.2020.100684] [PMID] [PMCID]
- [33] Scheim D. Ivermectin for COVID-19 treatment: Clinical response at quasi-threshold doses via hypothesized alleviation of CD147-mediated vascular occlusion [Internet]. 2020 [Updated 2021 August 22]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3636557 [DOI:10.2139/ssrn.3636557]
- [34] Rizzo E. Ivermectin, antiviral properties and COVID-19: A possible new mechanism of action. *Naunyn Schmiedeberg Arch Pharmacol*. 2020; 393(7):1153-6. [DOI:10.1007/s00210-020-01902-5] [PMID] [PMCID]

- [35] Priel A, Silberberg SD. Mechanism of ivermectin facilitation of human P2X4 receptor channels. *J Gen Physiol.* 2004; 123(3):281-93. [DOI:10.1085/jgp.200308986] [PMID] [PMCID]
- [36] Stokes L, Layhadi JA, Bibic L, Dhuna K, Fountain SJ. P2X4 receptor function in the nervous system and current breakthroughs in pharmacology. *Front Pharmacol.* 2017; 8:291. [DOI:10.3389/fphar.2017.00291] [PMID] [PMCID]
- [37] Shinohara EH, Martini MZ, de Oliveira Neto HG, Takahashi A. Oral myiasis treated with ivermectin: Case report. *Braz Dent J.* 2004; 15(1):79-81. [DOI:10.1590/S0103-64402004000100015] [PMID]
- [38] Pandey TR, Shrestha GB, Sitaula RK, Shah DN. A case of orbital myiasis in recurrent eyelid basal cell carcinoma invasive into the orbit. *Case Rep Ophthalmol Med.* 2016; 2016:2904346. [DOI:10.1155/2016/2904346] [PMID] [PMCID]
- [39] Basyoni MMA, El-Sabaa AAA. Therapeutic potential of myrrh and ivermectin against experimental *Trichinella spiralis* infection in mice. *Korean J Parasitol.* 2013; 51(3):297-304. [DOI:10.3347/kjp.2013.51.3.297] [PMID] [PMCID]
- [40] Tesh RB, Guzman H. Mortality and infertility in adult mosquitoes after the ingestion of blood containing ivermectin. *Am J Trop Med Hyg.* 1990; 43(3):229-33. [DOI:10.4269/ajtmh.1990.43.229] [PMID]
- [41] Chaccour C, Lines J, Whitty CJM. Effect of ivermectin on *Anopheles gambiae* mosquitoes fed on humans: The potential of oral insecticides in malaria control. *J Infect Dis.* 2010; 202(1):113-6. [DOI:10.1086/653208] [PMID]
- [42] Kobylinski KC, Deus KM, Butters MP, Hongyu T, Gray M, da Silva IM, et al. The effect of oral anthelmintics on the survivorship and re-feeding frequency of anthrophilic mosquito disease vectors. *Acta Trop.* 2010; 116(2):119-26. [DOI:10.1016/j.actatropica.2010.06.001] [PMID] [PMCID]
- [43] Kobylinski KC, Sylla M, Chapman PL, Sarr MD, Foy BD. Ivermectin mass drug administration to humans disrupts malaria parasite transmission in Senegalese villages. *Am J Trop Med Hyg.* 2011; 85(1):3-5. [DOI:10.4269/ajtmh.2011.11-0160] [PMID] [PMCID]
- [44] Panchal M, Rawat K, Kumar G, Kibria KM, Singh S, Kalamuddin M, et al. Plasmodium falciparum signal recognition particle components and anti-parasitic effect of ivermectin in blocking nucleo-cytoplasmic shuttling of SRP. *Cell Death Dis.* 2014; 5:e994. [DOI:10.1038/cddis.2013.521] [PMID] [PMCID]
- [45] Foy BD, Kobylinski KC, da Silva IM, Rasgon JL, Sylla M. Endectocides for malaria control. *Trends Parasitol.* 2011; 27(10):423-8. [DOI:10.1016/j.pt.2011.05.007] [PMID] [PMCID]
- [46] Mascari TM, Mitchell MA, Rowton ED, Foil LD. Ivermectin as a rodent feed-through insecticide for control of immature sand flies (Diptera: Psychodidae). *J Am Mosq Control Assoc.* 2008; 24(2):323-6. [DOI:10.2987/5678.1] [PMID]
- [47] Hanafi HA, Szumlas DE, Fryauff DJ, El-Hossary SS, Singer GA, Osman SG, et al. Effects of ivermectin on blood-feeding *Phlebotomus papatasi*, and the promastigote stage of *Leishmania major*. *Vector Borne Zoonotic Dis.* 2011; 11(1):43-52. [DOI:10.1089/vbz.2009.0030] [PMID]
- [48] Rasheid KA, Morsy TA. Efficacy of ivermectin on the infectivity of *Leishmania major* promastigotes. *J Egypt Soc Parasitol.* 1998; 28(1):207-12. [PMID]
- [49] Opara WEK, Ameh IG. Cutaneous leishmaniasis: a report of its treatment with Mectizan in Sokoto, Nigeria. *J Med Sci.* 2005; 5(3):186-8. [DOI:10.3923/jms.2005.186.188]
- [50] Distelmans W, D'Haeseleer F, Mortelmans J. Efficacy of systemic administration of ivermectin against tsetse flies. *Ann Soc Belg Med Trop.* 1983; 63(2):119-25. [PMID]
- [51] Pooda SH, Mouline K, De Meeüs T, Bengaly Z, Solano Ph. Decrease in survival and fecundity of *Glossina palpalis gambiense* vanderplank 1949 (Diptera: Glossinidae) fed on cattle treated with single doses of ivermectin. *Parasit Vectors.* 2013; 6:165. [DOI:10.1186/1756-3305-6-165] [PMID] [PMCID]
- [52] Dias JCP, Schofield CJ, Machado EM, Fernandes AJ. Ticks, ivermectin, and experimental Chagas disease. *Mem Inst Oswaldo Cruz.* 2005; 100(8):829-32. [DOI:10.1590/S0074-02762005000800002] [PMID]
- [53] Fallon PG, Doenhoff MJ. Drug-resistant schistosomiasis: Resistance to praziquantel and oxamniquine induced in *Schistosoma mansoni* in mice is drug specific. *Am J Trop Med Hyg.* 1994; 51(1):83-8. [DOI:10.4269/ajtmh.1994.51.83] [PMID]
- [54] Ismail M, Botros S, Metwally A, William S, Farghally A, Tao LF, et al. Resistance to praziquantel: Direct evidence from *Schistosoma mansoni* isolated from Egyptian villagers. *Am J Trop Med Hyg.* 1999; 60(6):932-5. [DOI:10.4269/ajtmh.1999.60.932] [PMID]
- [55] Mendonça-Silva DL, Pessôa RF, Noël F. Evidence for the presence of glutamatergic receptors in adult *Schistosoma mansoni*. *Biochem Pharmacol.* 2002; 64(9):1337-44. [DOI:10.1016/S0006-2952(02)01358-8]
- [56] Lynagh T, Lynch JW. Ivermectin binding sites in human and invertebrate Cys-loop receptors. *Trends Pharmacol Sci.* 2012; 33(8):432-41. [DOI:10.1016/j.tips.2012.05.002] [PMID]
- [57] Taman A, Ribeiro P. Characterization of a truncated metabotropic glutamate receptor in a primitive metazoan, the parasitic flatworm *Schistosoma mansoni*. *PLoS One.* 2011; 6(11):e27119. [DOI:10.1371/journal.pone.0027119] [PMID] [PMCID]
- [58] Taman A, El-Beshbishi S, El-Tantawy N, El-Hawary A, Azab M. Evaluation of the in vivo effect of ivermectin on *Schistosoma mansoni* in experimentally-infected mice. *J Coast Life Med.* 2014; 2(10):817-23. <https://www.researchgate.net/publication/263466782>
- [59] Alves SN, de Melo AL. Effects of benzodiazepine and ivermectin on *Girardiagrana* (Platyhelminthes: Turbellaria). *Biosci J.* 2013; 29(1):209-15. <https://seer.ufu.br/index.php/biosciencejournal/article/view/14413>
- [60] Mat'ha V, Weiser J. Molluscicidal effect of ivermectin on *Biomphalaria glabrata*. *J Invertebr Pathol.* 1988; 52(2):354-5. [DOI:10.1016/0022-2011(88)90146-2]
- [61] Sheele JM, Anderson JF, Tran TD, Teng YA, Byers PA, Ravi BS, et al. Ivermectin causes *Cimex lectularius* (bedbug) morbidity and mortality. *J Emerg Med.* 2013; 45(3):433-40. [DOI:10.1016/j.jemermed.2013.05.014] [PMID]
- [62] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020; 178:104787. [DOI:10.1016/j.antiviral.2020.104787] [PMID] [PMCID]

- [63] Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis.* 2021; 103:214-6. [DOI:10.1016/j.ijid.2020.11.191] [PMID] [PMCID]
- [64] Hellwig MD, Maia A. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. *Int J Antimicrob Agents.* 2021; 57(1):106248. [DOI:10.1016/j.ijantimicag.2020.106248] [PMID] [PMCID]
- [65] de Castro Jr CG, Gregianin LJ, Burger JA. Continuous high-dose ivermectin appears to be safe in patients with acute myelogenous leukemia and could inform clinical repurposing for COVID-19 infection. *Leuk Lymphoma.* 2020; 61(10):2536-7. [DOI:10.1080/10428194.2020.1786559] [PMID]
- [66] Popp M, Stegemann M, Metzendorf MI, Gould S, Kranke P, Meybohm P, et al. Ivermectin for preventing and treating COVID-19. *Cochrane Database Syst Rev.* 2021; 7(7):CD015017. [DOI:10.1002/14651858.CD015017] [PMID] [PMCID]
- [67] Barrows NJ, Campos RK, Powell ST, Prasanth KR, Schott-Lerner G, Soto-Acosta R, et al. A screen of FDA-approved drugs for inhibitors of Zika virus infection. *Cell Host Microbe.* 2016; 20(2):259-70. [DOI:10.1016/j.chom.2016.07.004] [PMID] [PMCID]
- [68] Ketkar H, Yang L, Wormser GP, Wang P. Lack of efficacy of ivermectin for prevention of a lethal Zika virus infection in a murine system. *Diagn Microbiol Infect Dis.* 2019; 95(1):38-40. [DOI:10.1016/j.diagmicrobio.2019.03.012] [PMID] [PMCID]
- [69] Ji W, Luo G. Zika virus NS5 nuclear accumulation is protective of protein degradation and is required for viral RNA replication. *Virology.* 2020; 541:124-35. [DOI:10.1016/j.virol.2019.10.010] [PMID]
- [70] Tay MYF, Fraser JE, Chan WKK, Moreland NJ, Rathore AP, Wang C, et al. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; Protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Res.* 2013; 99(3):301-6. [DOI:10.1016/j.antiviral.2013.06.002] [PMID]
- [71] Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J.* 2012; 443(3):851-6. [DOI:10.1042/BJ20120150] [PMID] [PMCID]
- [72] Surnar B, Kamran MZ, Shah AS, Basu U, Kolishetti N, Deo S, et al. Orally administrable therapeutic synthetic nanoparticle for Zika virus. *ACS Nano.* 2019; 13(10):11034-48. [DOI:10.1021/acsnano.9b02807] [PMID] [PMCID]
- [73] Mastrangelo E, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: New prospects for an old drug. *J Antimicrob Chemother.* 2012; 67(8):1884-94. [DOI:10.1093/jac/dks147] [PMID] [PMCID]
- [74] Götz V, Magar L, Dornfeld D, Giese S, Pohlmann A, Höper D, et al. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Scientific reports.* 2016; 6(1): 1-15. [DOI: <http://dx.doi.org/10.1038/srep23138>]
- [75] Wagstaff KM, Rawlinson SM, Hearps AC, Jans DA. An AlphaScreen®-based assay for high-throughput screening for specific inhibitors of nuclear import. *J Biomol Screen.* 2011; 16(2):192-200. [DOI:10.1177/1087057110390360] [PMID]
- [76] Azeem S, Ashraf M, Rasheed MA, Anjum AA, Hameed R. Evaluation of cytotoxicity and antiviral activity of ivermectin against Newcastle disease virus. *Pak J Pharm Sci.* 2015; 28(2):597-602. [PMID]
- [77] Ashraf Sh, Chaudhry U, Raza A, Ghosh D, Zhao X. In vitro activity of ivermectin against *Staphylococcus aureus* clinical isolates. *Antimicrob Resist Infect Control.* 2018; 7:27. [DOI:10.1186/s13756-018-0314-4] [PMID] [PMCID]
- [78] Tan X, Xie H, Zhang B, Zhou J, Dou Zh, Wang X, et al. A novel ivermectin-derived compound D4 and its antimicrobial/biofilm properties against MRSA. *Antibiotics.* 2021; 10(2):208. [DOI:10.3390/antibiotics10020208] [PMID] [PMCID]
- [79] Komiya Y, Habas R. Wnt signal transduction pathways. *Organogenesis.* 2008; 4(2):68-75. [DOI:10.4161/org.4.2.5851] [PMID] [PMCID]
- [80] Wang Y, Wang Sh, Lei M, Boyett M, Tsui H, Liu W, et al. The p21-activated kinase 1 (Pak1) signalling pathway in cardiac disease: From mechanistic study to therapeutic exploration. *Br J Pharmacol.* 2018; 175(8):1362-74. [DOI:10.1111/bph.13872] [PMID] [PMCID]
- [81] Allegra A, Pioggia G, Innao V, Musolino C, Gangemi S. New insights into YES-associated protein signaling pathways in hematological malignancies: Diagnostic and therapeutic challenges. *Cancers.* 2021; 13(8):1981. [DOI:10.3390/cancers13081981] [PMID] [PMCID]
- [82] Dou Q, Chen HN, Wang K, Yuan K, Lei Y, Li K, et al. Ivermectin induces cytostatic autophagy by blocking the PAK1/Akt axis in breast cancer. *Cancer Res.* 2016; 76(15):4457-69. [DOI:10.1158/0008-5472.CAN-15-2887] [PMID]
- [83] Diao H, Cheng N, Zhao Y, Xu H, Dong H, Thamm DH, et al. Ivermectin inhibits canine mammary tumor growth by regulating cell cycle progression and WNT signaling. *BMC Vet Res.* 2019; 15:276. [DOI:10.1186/s12917-019-2026-2] [PMID] [PMCID]
- [84] Nambara Sh, Masuda T, Nishio M, Kuramitsu Sh, Tobo T, Ogawa Y, et al. Antitumor effects of the antiparasitic agent ivermectin via inhibition of Yes-associated protein 1 expression in gastric cancer. *Oncotarget.* 2017; 8(64):107666-77. [DOI:10.18632/oncotarget.22587] [PMID] [PMCID]
- [85] Melotti A, Mas Ch, Kuciak M, Lorente-Trigos A, Borges I, Ruiz i Altaba A. The river blindness drug Ivermectin and related macrocyclic lactones inhibit WNT-TCF pathway responses in human cancer. *EMBO Mol Med.* 2014; 6(10):1263-78. [DOI:10.15252/emmm.201404084] [PMID] [PMCID]
- [86] Nishio M, Sugimachi K, Goto H, Wang J, Morikawa T, Miyachi Y, et al. Dysregulated YAP1/TAZ and TGF- β signaling mediate hepatocarcinogenesis in Mob1a/1b-deficient mice. *Proc Natl Acad Sci U S A.* 2016; 113(1):E71-80. [DOI:10.1073/pnas.1517188113] [PMID] [PMCID]
- [87] Zhu M, Li Y, Zhou Zh. Antibiotic ivermectin preferentially targets renal cancer through inducing mitochondrial dysfunction and oxidative damage. *Biochem Biophys Res Commun.* 2017; 492(3):373-8. [DOI:10.1016/j.bbrc.2017.08.097] [PMID]
- [88] Nappi L, Aguda AH, Al Nakouzi N, Lelj-Garolla B, Beraldi E, Lallous N, et al. Ivermectin inhibits HSP27 and potentiates

- efficacy of oncogene targeting in tumor models. *J Clin Invest.* 2020; 130(2):699-714. [DOI:10.1172/JCI130819] [PMID] [PMCID]
- [89] Sharmeen S, Skrtic M, Sukhai MA, Hurren R, Gronda M, Wang X, et al. The antiparasitic agent ivermectin induces chloride-dependent membrane hyperpolarization and cell death in leukemia cells. *Blood.* 2010; 116(18):3593-603. [DOI:10.1182/blood-2010-01-262675] [PMID]
- [90] Zhang P, Zhang Y, Liu K, Liu B, Xu W, Gao J, et al. Ivermectin induces cell cycle arrest and apoptosis of HeLa cells via mitochondrial pathway. *Cell Prolif.* 2019; 52(2):e12543. [DOI:10.1111/cpr.12543] [PMID] [PMCID]
- [91] Gallardo F, Teiti I, Rochaix Ph, Demilly E, Jullien D, Mariamé B, et al. Macrocyclic lactones block melanoma growth, metastases development and potentiate activity of anti-BRAF V600 inhibitors. *Clin Skin Cancer.* 2016; 1(1):4-14.e3. [DOI:10.1016/j.clsc.2016.05.001]