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

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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, antivirus, 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], antivi-

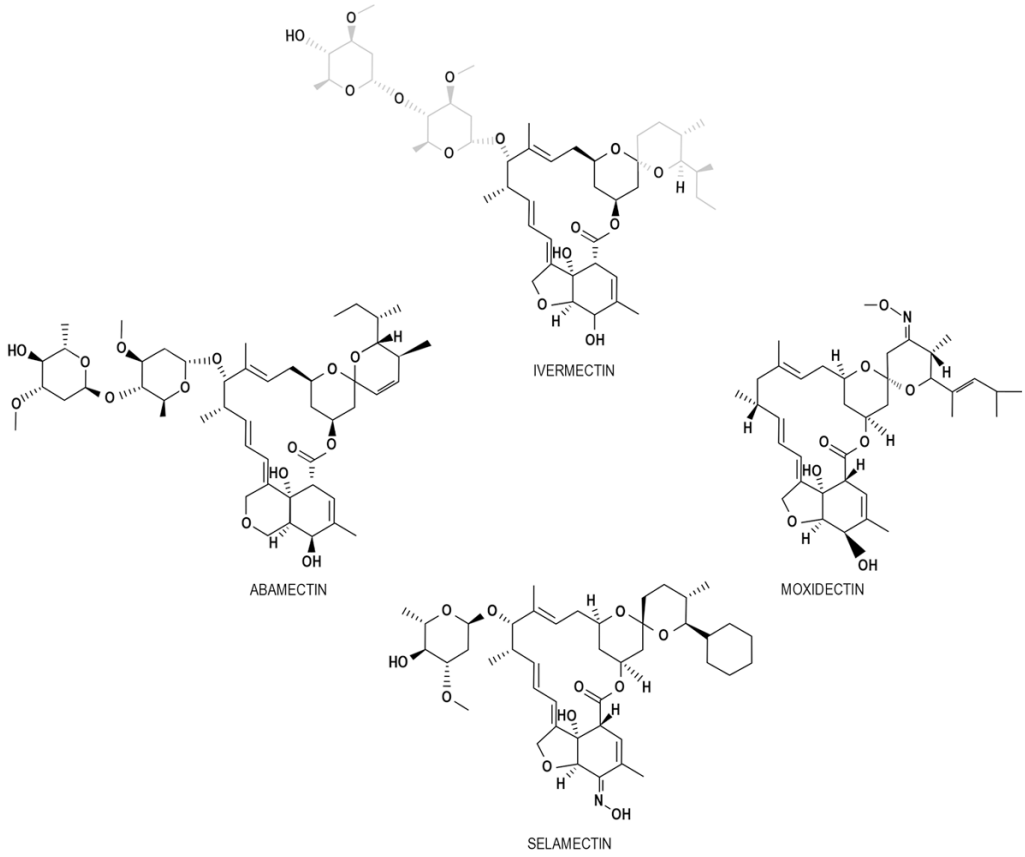

Figure 1. Most popular compounds of the AVM class. Note that all of them have bisoleandrosyloxy substituent at C13 with 16-carbon macrocyclic lactone core. IUPAC name of ivermectin is 22,23-dihydroavermectin B1a + 22,23-dihydroavermectin B1b.

ral activities [27] (e.g. HIV[1], 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, increasing C-reactive protein and Interlukin-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 IMPα/β1-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 $P2X_4$ receptor. P2X receptors are ATP-gated channels which are selective for cations [35]. They moderate several functions via extracellular ATP [36]. $P2X_4$, 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

1. Human Immunodeficiency Virus

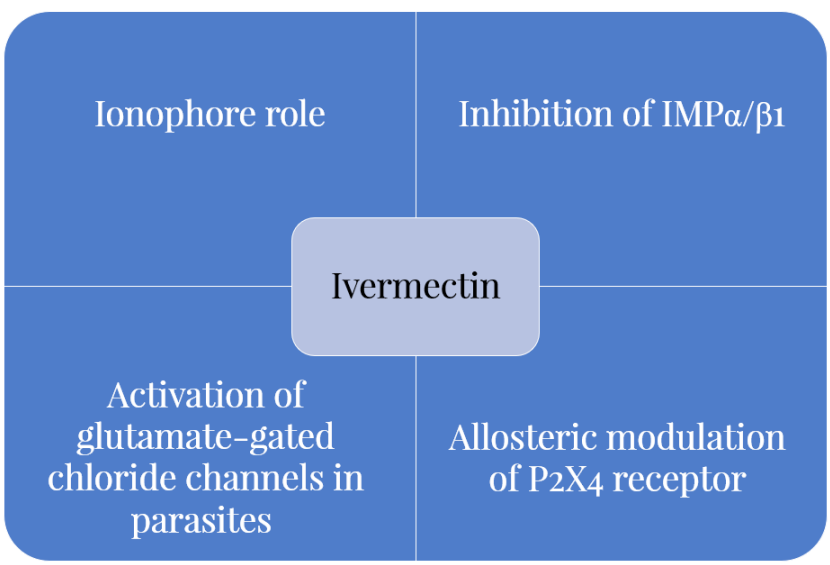

Figure 2. Proposed mechanisms of ivermectin

[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 leishmaniosis in eliminating *Leishmania tropica* [44]. In combination with surgical wound dressing, ivermectin holds great promise to cure cutaneous leishmaniosis [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 diseasecaused 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 invermectin 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. NS5[2] 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 IMPα/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 µg/ml have cytotoxic effects. Nevertheless, the safe concentration of ivermectin was at 50 µg/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 µg ml^{-1} and 20 µg 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 Ca^{2+} homoeostasis-related cardiac arrhythmias, adrenergic stress- and pressure overload-induced hypertrophy, and ischaemia/reperfusion injury [80]. The Hippo/YES-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.

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Author's contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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