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Ivermectin for COVID-19: a broad-spectrum veterinary endectocide with antiviral activity

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Abstract

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is a novel zoonotic coronavirus that has emerged from Wuhan, China. Compared to its predecessors, Severe Acute Respiratory Syndrome CoV (SARS-CoV) and Middle East Respiratory Syndrome CoV (MERS-CoV), SARS-CoV-2 has exhibited efficient human-to-human transmission. In addition to the efficient human-to-human transmission, SARS-CoV-2 is also reported to infect other animal species such as cats, tigers, lions, dogs, and minks. The susceptibility of other felines such as cheetah, puma, jaguar, leopard, and lynx are unknown. The reports of SARS-CoV-2 natural infection in animals opens up several opportunities to identify suitable animal models for the evaluation of SARS-CoV-2-specific vaccines and therapeutics. Ivermectin is a macrocyclic lactone endectocide that has broad-spectrum anti-parasitic activity. The wonder drug ivermectin was also found to possess anti-viral, anti-bacterial, and anti-cancer activity. The antiviral activity exhibited by ivermectin against SARS-CoV-2 is believed to be mediated via targeting the importin α/β -mediated nuclear transport and requires further validation. Since, the antiviral activity of ivermectin is through a host-directed mechanism, it can reduce the viral load even if administered at a lower dose. Further studies are required to evaluate the efficacy of ivermectin based on *in vivo* as well as the clinical trials. Being an FDA approved antiparasitic drug, repurposing it for treating COVID-19 patients will be an easy task once it is found to have therapeutic potential.

Keywords: Ivermectin; SARS-CoV-2; COVID-19; Repurposed drugs; Therapeutics; Antiviral drug

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Introduction

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is the third zoonotic coronavirus (CoV) after Severe Acute Respiratory Syndrome CoV (SARS-CoV) and Middle East Respiratory Syndrome CoV (MERS-CoV) (Dhama et al., 2020a; Malik et al., 2020a). SARS-CoV-2 has exhibited very high transmission potential among human beings (Dhama et al., 2020a). Bats are considered to be the reservoir host and the most probable source of origin in case of SARS-CoV-2 (Malik et al., 2020a). The genome of SARS-CoV-2 was found to be more similar to SARS-CoV than MERS-CoV at the nucleotide level (Sharun et al., 2020a). In addition to the efficient human-to-human transmission, SARS-CoV-2 is also reported to infect other species such as cats (Rodriguez-Morales et al., 2020), tigers, lions (Sharun et al., 2020b), dogs, and minks (Dhama et al., 2020b; Tiwari et al., 2020). The superior transmission potential exhibited by SARS-CoV-2 as compared to SARS-CoV and MERS-CoV warrants the need for implementing biosafety and biosecurity measures to control and prevent the disease transmission among human beings and animals (Ahmad et al., 2020; Sivaprasad et al., 2020).

Researchers are trying to develop SARS-CoV-2-specific vaccines and therapeutics to counter this pandemic. A few of these candidate vaccines and therapeutics are already undergoing clinical trials and have shown promising results (Haritha et al., 2020; Malik et al., 2020b; Patel et al., 2020). Some of the repurposed drugs include ivermectin, dexamethasone, ebiselen etc (Haritha et al., 2020; Sharun et al., 2020c; Sharun et al., 2020d). Antibody-based immunotherapeutic strategies such as convalescent plasma and monoclonal antibodies was found to be associated with reduction in the mortality rate among COVID-19 patients (Sharun et al., 2020e).

The review is aimed to analyze and evaluate the potential of ivermectin as an antiviral agent against SARS-CoV-2. We have also discussed in brief about the occurrence of SARS-CoV-2 infection in animal species.

COVID-19 in animals

Although several reports of SARS-CoV-2 infection has been reported in companion animals like dog and cats, none of them could establish the effective transmission of this novel virus from animals-to-humans (Sharun et al., 2020a; Tiwari et al., 2020). On 4th April 2020, the first case of COVID-19 in zoo animals was confirmed in a Malayan tiger maintained at the Bronx Zoo, New York (CDC, 2020). The samples were taken for testing when several big cats started showing signs of respiratory illness. Recently another four tigers and three lions from the same zoo were

tested positive for COVID-19, increasing the total number of SARS-CoV-2 positive zoo animals to eight (National Geographic, 2020). Experts believe that these big cats got the disease from a COVID-19 positive zoo employee (CDC, 2020). Even though several animals exhibited clinical signs, samples from only one tiger were collected for testing as it required general anesthesia (Shi et al., 2020). Later, additional tests were done in the suspected animals using fecal samples (National Geographic, 2020).

The potential for animal-to-animal transmission has already been reported in cats under experimental conditions (USDA, 2020). Therefore, social distancing has to be followed not only in human beings but also for animals, especially those animals that are maintained in zoos. Big cats living in confined enclosures are at higher risk of getting COVID-19. Even though animal-to-animal transmission is not reported under natural conditions, the possibility for the same cannot be ruled out. The occurrence of SARS-CoV-2 infection in the captive population of big cats gives us a hint on the possibility of disease spill-over to the wild populations of tigers and lions. Such a scenario will threaten the survival and damage the future of these wild animal species. As of now, domestic cat, tiger, and lions are found to be susceptible to SARS-CoV-2 infection. The susceptibility of other felines such as cheetah, puma, jaguar, leopard, and lynx are unknown. The reports of SARS-CoV-2 natural infection in animals opens up several opportunities to identify suitable animal models for the evaluation of SARS-CoV-2-specific vaccines and therapeutics. The efficacy and safety of COVID-19 vaccines are mainly evaluated using non-human primates, Rhesus macaque (*Macaca mulatta*) and Cynomolgus macaque (*Macaca fascicularis*) (Faslu Rahman et al., 2020; Sharun et al., 2020b).

Ivermectin for COVID-19

Caly et al. (2020) recently reported that the veterinary drug ivermectin exhibited *in vitro* antiviral activity against SARS-CoV-2, the virus responsible for Coronavirus disease 2019 (COVID-19). This is a proud moment for veterinary dermatologists around the world. Ivermectin, a macrocyclic lactone endectocide, is considered as the “wonder drug” in veterinary dermatology due to its broad-spectrum anti-parasitic activity. This great drug was first introduced to the animal health market as an endectocide in the year 1981 (Omura and Crump, 2014). Following its commercialization. Ivermectin was initially used as an endectocide that is effective against both ectoparasitic arthropods and endoparasitic nematodes of animals (Sharun et al., 2019a). Ivermectin has been used in therapeutics of parasitic skin conditions such as

demodicosis and sarcoptic mange with excellent efficacy (Paterson et al., 2009; Vine et al., 2010; Sharun et al., 2019a). The antiparasitic activity of ivermectin is mediated by selectively binding to the glutamate-gated chloride channels, thereby increasing the permeability of chloride ions resulting in motor paralysis and death (Omura and Crump, 2014).

However, as time passed, ivermectin was found to possess anti-viral, anti-bacterial, and anti-cancer potential that further extended the activity spectrum of this wonder drug (Omura and Crump, 2014; Sharun et al., 2019b). During the past 40 years following its introduction, ivermectin has been extensively evaluated as a repurposed therapeutic drug against several bacterial and viral diseases of both animals and human beings (Crump, 2017). The clinical utility of ivermectin has significantly been hampered due to its potential for cytotoxicity. However, this can be controlled by changing the vehicles used in the formulations, thereby modifying the pharmacokinetic properties of the drug (Sharun et al., 2019b).

The broad-spectrum antiviral activity exhibited by ivermectin against several animal and human viruses are mediated via targeting major components/processes like importin α/β -mediated nuclear transport, nuclear import of UL42, NS3 helicase, and nuclear localization signal-mediated nuclear import of Cap (Sharun et al., 2020c). However, the antiviral activity exhibited by ivermectin against several RNA viruses is mediated by the inhibition of importin α/β -mediated nuclear transport (Crump, 2017). An analogous process has been suggested for the anti-SARS-CoV-2 activity exhibited by ivermectin and requires further validation (Caly et al., 2020). The antiviral activity of ivermectin is mediated by directly targeting a key cellular process of the mammalian cell instead of the virus. Being a host-directed agent (HDA), administration of ivermectin at lower doses will be sufficient enough to reduce the viral load by a modest amount. This will give sufficient time for the body's immune system to mount full scale antiviral response against SARS-CoV-2 (Bray et al., 2020).

Figure 1: Ivermectin exerts antiviral activity against SARS-CoV-2 via targeting the importin α/β -mediated nuclear transport. IMP α/β 1 binds to the CoV protein in the cytoplasm and translocate it through the nuclear pore complex (NPC) into the nucleus leading to enhanced infection. Ivermectin binds and destabilises the IMP α/β 1 heterodimer thereby preventing IMP α/β 1 from binding to the viral protein and preventing it from entering the nucleus thereby leading to efficient antiviral activity.

Conclusion and future prospects

The increasing reports of COVID-19 in animals, especially in zoo animals, should be considered as a matter of great concern in terms of animal health, welfare, and wildlife conservation. The recent developments in the animal susceptibility to COVID-19 calls for the implementation of strict surveillance and routine screening in zoo animals all around the world. In addition to the disease surveillance in zoo animals, zookeepers and employees should be screened to prevent the possibility of human-to-animal transmission. Taking into consideration the susceptibility of felines to SARS-CoV-2, disease surveillance and screening should be extended to the other members of the family Felidae.

Further studies are going on at the moment to evaluate *in vivo* as well as the clinical utility of ivermectin to counter this pandemic virus. Being an FDA approved antiparasitic drug, repurposing ivermectin for the treatment of COVID-19 patients will be an easy task if found useful in the clinical trials. Apart from the well-established clinical utility in veterinary dermatology clinics, ivermectin will continue to surprise the scientific world by further expanding its activity spectrum against diverse ranges of emerging and re-emerging diseases.

Authorship contribution statement

Khan Sharun: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **C. K. Faslu Rahman:** Software, Writing - review & editing. **Bosco Jose:** Writing - review & editing. **Irshad A:** Writing - review & editing. **Kuldeep Dhama:** Writing - review & editing. **Ruchi Tiwari:** Writing - review & editing. **Alfonso J. Rodriguez-Morales:** Writing - review & editing.

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Declaration of Competing Interest

All authors declare that there exist no commercial or

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