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A Wonder Drug in the Arsenal against COVID - 19: Medication Evidence from Ivermectin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors were involved in designing the framework, literature search and contributed for writing the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Ivermectin, an FDA approved broad-spectrum anti-parasitic agent has been recently reported to show an inhibitory activity against SARS-CoV-2 in an in-vitro study. This antiviral response has rendered it as a potential drug to be repurposed for COVID-19. Previously, ivermectin had showed inhibitory activity against RNA viruses in-vitro and DNA viruses in-vitro and in-vivo respectively. Much of its characterization has been related to SARS-CoV wherein viral proteins interacting with IMPα/β1 (Importins) were proposed to enhance the viral infectivity. These documentations serve as a ray of hope for considering ivermectin in treating COVID-19 due to its suggested nuclear transport inhibitory mechanism. Importantly, these recent findings warrant detailed investigations for understanding its benefit in terms of efficacy and safety in COVID-19 patients. This review article throws light on the current consensus in this regard.

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ABBREVIATIONS

ACE2	*: Angiotensin-Converting Enzyme 2*
ARDS	*: Acute Respiratory Distress Syndrome*
AT2	*: Alveolar Type 2*
COVID-19	*: Corona Virus Disease-2019*
EBOV	*: Ebola Virus Disease*
FDA	*: Food and Drug Administration*
IMP	*: Importins*
IN	*: Integrase Proteins*
MERS	*: Middle East Respiratory Syndrome*
PRV	*: Pseudorabies Virus*
SARS	*: Severe Acute Respiratory Syndrome*
TMPRSS2	*: Transmembrane Protease Serine 2*
VEEV	*: Venezuelan Equine Encephalitis Virus*
WHO	*: World Health Organization*
Level of Evidence	*: Level I*

1. INTRODUCTION

Apart from Penicillin and Aspirin, Ivermectin (22,23-dihydroavermectin B) claimed the name of "Wonder drug" [1]. In the late-1970s, Ivermectin revolutionized the treatment of tropical diseases in terms of versatility, safety and the its beneficial impact on the mankind. Ivermectin had a wide range of anti-microbial activity for treating and controlling tropical diseases caused by the gastrointestinal roundworms, lungworms, nematodes, mites, lice, ticks and house flies [2]. Ivermectin gained the name "The Blockbuster Drug" in animal husbandry and aquaculture industry [2]. The novel drug ivermectin helps in combating the diseases which represents one of the most triumphant public health campaigns across the globe. Despite approaching 25 years of widespread human usage, no resistance to ivermectin has yet appeared to minimise its impact in disease control programmes of public health importance.

The global response to COVID-19 pandemic is currently confined to monitoring, supportive care and containment strategies. Numerous clinical trials are underway to evaluate the plausible therapies against SARS-CoV-2. In the context of COVID-19 drug therapy, recently it has been reported that Ivermectin showed inhibitory activity against SARS-CoV-2 in an in-vitro study by Caly et al. (2020) [3]. Amidst this pandemic scenario, this turned out to be a wave of resonance among the press globally [4].

This discovery definitely renders a beacon of hope but at the same time addresses a word of caution for its off-label and compassionate utility especially when it comes for treating critically ill-patients [5]. In fact, it is important to review critically and diligently before considering for severe cases as hyper inflammatory state increases the risk of neurotoxicity as per its mechanism and secondly warrants more caution when used concomitantly with other antiviral drugs [6-9]. In this review article we sought to discuss the current consensus on the antiviral response of Ivermectin in terms of its plausibility to subjugate COVID-19.

2. MATERIALS AND METHODS

For the duration between March 2020 and May 2020, we conducted a scoping review from PubMed, Google Scholar, Scopus, PubMed Central and Medline using the following search terms namely Ivermectin & Parasites, Ivermectin & Viruses, Ivermectin & Bacteria, drugs for COVID-19, and Ivermectin in COVID-19. A total of 91 articles were found. Two independent reviewers collected the articles and a total of 55 articles were finally chosen for the review. A framework was developed for analysis of the articles and then the antiviral response of Ivermectin was correlated with previous in-vitro studies on viruses.

3. RESULTS

A scoping review revealed that ivermectin has demonstrated inhibitory effects against RNA and DNA viruses, thereby opening the doors for further research and development particularly in treating the respiratory viral infections.

3.1 Ivermectin Pharmacology

Ivermectin, which is derived from the bacterium Streptomyces avermitilis, is a potent macrocyclic lactone compound [10,11]. It kills the ecto- and endoparasites by interfering with nervous system and muscular functioning by enhancing its inhibitory neurotransmission. Ivermectin binds to glutamate-gated chloride channels (GluCls) in the membranes of nerve and muscle cells, causing increased permeability to chloride ions, resulting in cellular hyper-

polarization, followed by paralysis and death [12]. It does not readily cross the blood–brain barrier of mammals due to the presence of P-glycoprotein [13].

Ivermectin is a cytochrome P450 (CYP)3A4 substrate. The oral administration of ivermectin yields 50–60% bioavailability and it attains peak levels by 4–5 hours following single dose. The drug is metabolized in the liver and the excretion of metabolites occurs primarily via feces (98%) and urine (1%). The half-life of the parent drug is 12–56 hours and the half-life of its metabolites is up to 3 days. In some patients, secondary peak in plasma levels can occur between 6 and 12 hours following dosing due to enterohepatic cycle [14,15]. Ivermectin was unprecedented, effective orally, topically or parenterally and at very low doses. It has been proven as a potent antimicrobial agent for varied microbial spectra.

3.2 Ivermectin and Anti-microbial Cross-talks

3.2.1 Anti-parasitic

They were radically different and lacked cross-resistance with any existing commonly used antiparasitic compounds, macrocyclic lactones apparently devoid of antibacterial or antifungal properties but active against nematodes found in all major segments of the gastrointestinal tract, and against organisms known to be resistant to benzimidazole antihelmintics [16]. Ivermectin has been used in wide range of diseases such as Onchocerciasis (mass drug administration) [17], Strongyloidiasis (single dose proven effective in clearing the parasite [18], Scabies (0.8% lotion and oral ivermectin) [19], Pediculosis (superiority of oral ivermectin over 0.5% lotion formulation) [20], Gnathostomiasis (superiority of oral ivermectin (95.2%) over albendazole (93.8%) in terms of cure rate) [21], Myiasis (oral ivermectin proven effective than manual removal of maggots) [22], Mansonellosis (single dose causing long-term suppression of microfilariae) [23], Trichinellosis (ivermectin tested against adult trichinella worms at day 0 and day 5 and encysted larvae on day 15 and day 35 post-infection showed significant reduction in worm and larvae load and proven efficacious) [24], Ascariasis (combination treatment of ivermectin + albendazole significantly proven higher cure and egg reduction rates than diethylcarbamazine) [25], Trichuriasis (Ivermectin monotherapy showed significant results against worm clearance and egg reduction rates) [26], Malaria (at submicromolecular levels, ivermectin inhibits the nuclear import of polypeptides of the signal recognition particle of *P. falciparum* (PfSRP)) [27], Trypanosomiasis (In experiments mice, ivermectin proved effective in killing tse tse fly vectors of Trypanosoma brucei brucei parasites that cause sleeping sickness) [28] and Leishmaniasis (neglected tropical disease, where ivermectin is more effective in killing promastigotes of Leishmania major compared with rifampicin, nystatin, and erythromycin) [29].

3.2.2 Anti-viral

Recently, Ivermectin was found to be a broad spectrum inhibitor of importin α/β nuclear import. It disrupts HIV-1 integrase in HIV-1 and NS-5 polymerase & NS-3 helicase in dengue viruses [30]. Ivermectin targets NS-3 helicase activity in Japanese encephalitis, and tick-borne Encephalitis [31]. Ivermectin proved to show an inhibitory potential towards dengue by interrupting viral replication and hence by offering protection against all dengue serotypes [32]. In 2015, Carocci et al proved that IC50 values of ivermectin against yellow fever virus, dengue virus and West Nile virus helicases were 0.12 μM, 0.5 μM and 0.35 μM, respectively [33]. Ivermectin showed strong antiviral activity (>85% inhibition of CHIKV-RLuc signal) against chikungunya virus. It downregulated the viral protein expression and mature virion formation effectively [34]. Cytotoxic and antiviral potential of ivermectin and ribavirin on Newcastle virus were evaluated. The results showed that ivermectin was safe and cytotoxic at ≤ 50 μg/ml and 100μg/ml concentrations respectively. Ivermectin had strong antiviral potential at 100μg/ml and higher but same concentrations were cytotoxic [35].

3.2.3 Anti-bacterial

In 2012, researchers proved that ivermectin has the ability of preventing infection of epithelial cells by Chlamydia trachomatis [36]. In 2013, researchers further reported that ivermectin showed a mycobactericidal effect against multidrug resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis [37].

3.3 Ivermectin: Target Action in COVID-19

SARS-CoV-2 is the causative agent for COVID-19 pandemic and studies have found it to be

closely related to SARS-CoV. It is a single stranded, non-segmented RNA virus sharing analogy to SARS-CoV in terms of molecular entry mechanism. Few studies on SARS-CoV proteins have brought out the role of importins (IMPα/β1) whilst infection wherein the nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein and this in turn affect host cell division. Additionally, antagonising role of ORF6 (accessory protein of SARS-CoV) to bring down antiviral activity of transcription factor (STAT1) has been shown [38-42]. All these corroborate for ivermectin's inhibitory activity of nuclear transportation.

IMPα/β1 heterodimer plays important role in this regard. In the cytoplasm, it binds to the coronavirus cargo protein to translocate it through a complex called NPC (Nuclear Pore Complex) and thereby enters into the nucleus. Then this complex falls apart and further the viral cargo enhances infection due to reduction in host cell antiviral response. On the other hand in the presence of ivermectin, its binding destabilises the Impα/β1 heterodimer and prevents its binding with the viral protein. This in turn bars it from entering into the nucleus. As a result, a normal or more efficient antiviral response is seen and hence ivermectin's clinical utility can be extended for treating COVID-19. The schematic representation of the same has been demonstrated in Fig. 1.

3.4 Ivermectin and SARS-CoV-2

Ivermectin reported to inhibit the replication of SARS-CoV-2 in monkey kidney cell culture with an IC_{50} of 2.2 - 2.8 μM thereby making it a plausible drug for nCOVID-19 repurposing research [43]. Caly et al., [3] demonstrated antiviral action of ivermectin against the SARS-CoV-2 clinical isolate in vitro. With a single dose of the drug, the team reported 5000 – fold reduction in the RNA levels of SARS-CoV-2 in comparison to those in control group following infection and incubation of Vero/hSLAM cells with 5 μM ivermectin for 48 hours [3]. The authors hypothesized that such results were likely due to the inhibition of importin-α/β1 mediated nuclear import of viral proteins, as shown for other RNA viruses. However, no study with ivermectin *in vivo* has been conducted.

The doses used in cell culture seemingly require 10^4 larger doses in humans as per this data and for this reason it doesn't make it a promising drug candidate for an effective treatment of COVID-19 [44]. The FDA has issued guidance for not using ivermectin intended for animals as treatment for COVID-19 in humans (on 10th April, 2020) [45].

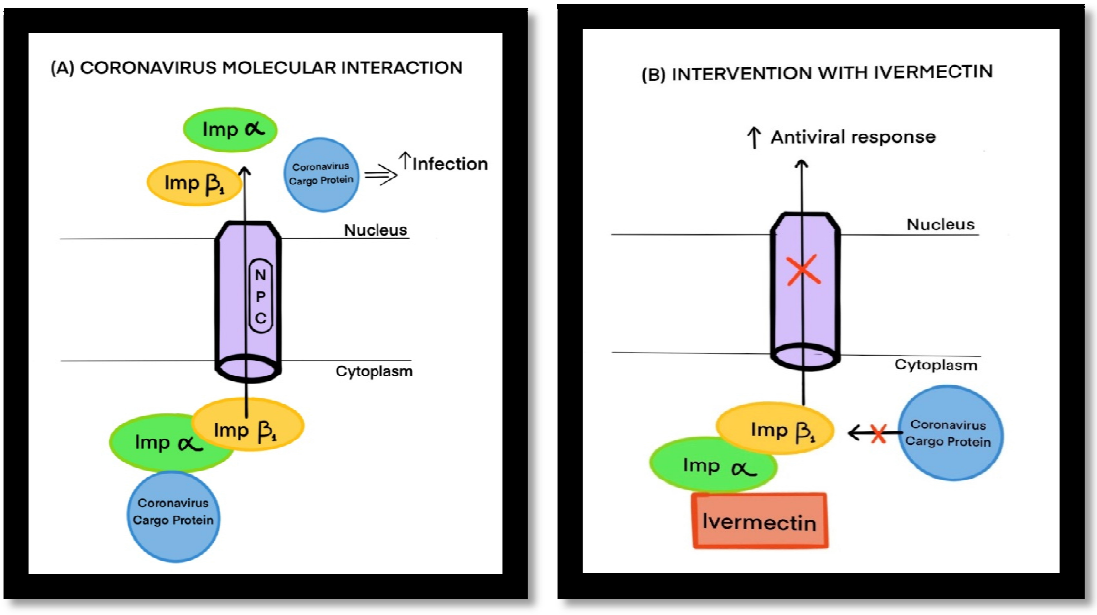

Fig. 1. Schematic representation of intervention with Ivermectin against coronavirus

[(a) IMPα/β1 heterodimer interaction with SARS-CoV Cargo Protein and facilitation of entry into nucleus through NPC whereby enhancing viral infectivity; (b) Intervention with ivermectin which prevents the entry of SARS-CoV cargo protein into the nucleus and thereby increases the antiviral response]

The Health Department of the Republic of Peru (on 8th May, 2020) approved ivermectin for treatment of COVID-19 in humans [46].

4. DISCUSSION

A long dated history of ivermectin exemplifies its effective clinical utility in treating and controlling several tropical diseases [16]. Interestingly, in recent years it has demonstrated antiviral response against wide range of viruses *in-vitro* [32,47,48]. Wagstaff et al., (2011) described ivermectin to play inhibitory role between the HIV-1 integrase and importins α/β1 heterodimer facilitating integrase nuclear import [30] and Wagstaff et al., (2012) confirmed the same.[30,49] Since then ivermectin has reported inhibitory effect against many RNA viruses like DENV 1-4, West Nile Virus, Venezuelan equine encephalitis virus (VEEV) and Influenza [30,32,47-50]. Similarly ivermectin showed inhibitory activity both *in-vitro* and *in-vivo* against DNA virus PRV (*Psuedorabies* Virus) and to add on, treatment with ivermectin in PRV - infected mice showed increased survival [51]. At present, the characterization of this newly emerged strain of coronavirus has been closely linked to SARS-CoV responsible for SARS outbreak in 2002-2003. The molecular studies on SARS-CoV highlighted the key role of IMPα/β1 and how the viral proteins interplay to enhance viral infectivity. Further Frieman et al., (2007), brought out the antagonising role of accessory protein ORF6 of SARS-CoV [38-42,52]. On the contrary, a clinical trial in Thailand including intervention with ivermectin for treating dengue fever reported it to be safe but did not demonstrate any clinical benefits [53]. These findings have popularised mixed views that are not concrete enough to direct ivermectin for treating COVID-19 patients. The limitations of these available evidences warrant critical analysis with further undertaking of investigations to overcome the same.

Ivermectin 12 mg as a single dose is being used in few tertiary care centres with a good clinical response but we staunchly believe that these recent fi12 mg a in context to ivermectin should be advocated with rapid implementation of controlled clinical trials in order to assess its efficacy and safety for treating COVID-19. Currently 9 studies are enrolled on *Clinicaltrials.gov* which includes ivermectin as an intervention for COVID-19 and of these only 3 studies (NCT04343092, NCT04373824 and NCT04374019) are currently recruiting participants [54]. Notably, the study coded NCT04373824 entitled as 'Max Ivermectin-COVID 19 Study Versus Standard of Care Treatment for COVID 19 Cases. A Pilot Study (MHC-COVID-19INV- ACT-BHR)' is an Indian set-up based interventional study (Open label, Non-randomized controlled trial) with enrollement of 50 participants respectively. This study will be completed at the earliest by July, 2020 among these recruiting studies. Overall, these serve as a shaft of light in the dark times of pandemic. These trials which are underway may open the doors for a new ground of research especially on the potential use of antiparasitic drugs like ivermectin and related compounds, including compounds as antiviral drugs. At the same time; two important aspects should be critically and diligently analysed before considering it for severe cases [6-9].

1. Ivermectin may cross-target the GABA-gated chlorine channels in CNS and may cause neurotoxicity by crossing attenuated BBB (blood-brain barrier) due to hyper inflammatory state.
2. The major metabolic pathway of ivermectin is P4503A4 and on the other hand drugs like lopinavir/ritonavir or darunavir/cobicistat inhibit P4503A4. Therefore, their concurrent utilization will increase systemic exposure of ivermectin; thereby warrant extreme attention on this aspect.

An alternative to address the above enlisted issue is by considering evaluating ivermectin's virological outcomes among uncomplicated and low-risk patients early in the course of the disease at first. The consideration should be made for conducting clinical trials under due ethical regard involving vast pharmacokinetic models for validating its impact before rationalizing and implementing it for treating COVID-19 patients.

5. CONCLUSION

From past 25 years of experience, no resistance to this novel drug, ivermectin has been reported in humans for tropical diseases. The discovery of antiviral activity of ivermectin against COVID-19 renders a beacon of hope but at the same time its off-label and compassionate utility demands careful risk-benefit analysis especially in those who are critically ill. Evaluating virological outcomes in uncomplicated and low-risk patients initially serves a better alternative for its concrete work-up. Until the results of a well-conducted

clinical trials are available, the drug should be avoided for treating COVID-19 patients routinely. Clinicians should advocate treatment in conjunct with rapidly emerging literature in this connotation in a wiser manner.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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