The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article

15 June 2021

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The Journal of Antibiotics (2021)Cite this article

22 June 2021 Editor's Note: Readers are alerted that the conclusions of this paper are subject to criticisms that are being considered by the editors and the publisher. A further editorial response will follow the resolution of these issues.

Abstract

Considering the urgency of the ongoing COVID-19 pandemic, detection of various new mutant strains and future potential re-emergence of novel

coronaviruses, repurposing of approved drugs such as Ivermectin could be worthy of attention. This evidence-based review article aims to discuss the mechanism of action of ivermectin against SARS-CoV-2 and summarizing the available literature over the years. A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications have been proposed.

Introduction

A relatively recent surge in zoonotic diseases has been noted over the past few decades. Several reasons could be responsible for this “spill-over” of disease-causing agents from animals to humans. These include an exponential rise in the global population causing man to encroach new ecological habitats in search of space, food, and resources as well as improved opportunities for rampant wildlife trade causing inter-species pathogen jumps. The 1980s was known for HIV/AIDS crisis that originated from the great apes, while the Avian flu pandemic in 2004-07 came from the birds. The pigs lead to the Swine flu pandemic in 2009 and bats were the original hosts of Ebola, Severe Acute Respiratory Syndrome (SARS), Middle Eastern respiratory syndrome (MERS), and probably Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) outbreak as well.

COVID-19 has already caused millions of deaths worldwide and has paralyzed not only the world’s healthcare system but also the political and economic relations between countries [1]. The fact that the SARS-CoV-2 virus has been thought to have originated from wildlife and may have “jumped” into humans, not only highlights future risks from animal-borne diseases but also provides an important clue to its resolution. In such a scenario, where this “jump” has been made from animal to human, it seems only logical to review a drug that has worked efficiently against a disease-

causing agent and is available in a form that is safe for human consumption since the early 1980 s.

Ivermectin belongs to a group of avermectins (AVM), which is a group of 16 membered macrocyclic lactone compounds discovered at the Japanese Kitasato institute in 1967 during actinomycetes cultures with the fungus *Streptomyces avermitilis* [2]. This drug radically lowered the incidence of river blindness and lymphatic filariasis and was discovered and developed by William C. Campbell and Satoshi Ōmura for which they received the Nobel Prize in Physiology or Medicine in 2015 [3, 4]. Ivermectin is enlisted in the World Health Organization's Model List of Essential Medicines [5].

Drug repurposing, drug redirecting, or drug reprofiling is defined as the identification of novel usages for existing drugs. The development risks, costs as well as safety-related failure, are reduced with this approach since these drugs have a well-established formulation development, in vitro and in vivo screening, as well as pharmacokinetic and pharmacodynamic profiles. Moreover, the first clinical trial phases of many such drugs have been completed and can be bypassed to reduce several years of development. Therefore, drug repurposing has the potential to reduce the time frame for the whole process by up to 3–12 years and carries great potential [6].

Although several drugs received Emergency Use Authorization for COVID-19 treatment with unsatisfactory supportive data, Ivermectin, on the other hand, has been sidelined irrespective of sufficient convincing data supporting its use. Nevertheless, many countries adopted ivermectin as one of the first-line treatment options for COVID-19.

With the ongoing vaccine roll-out programs in full swing across the globe, the longevity of the immunity offered by these vaccines or their role in offering protection against new mutant strains is still a matter of debate. The

adoption of Ivermectin as a “safety bridge” by some sections of the population that are still waiting for their turn for vaccination could be considered as a “logical” option.

Several doctor-initiated clinical trial protocols that aimed to evaluate outcomes, such as reduction in mortality figures, shortened length of intensive care unit stay and/or hospital stay and elimination of the virus with ivermectin use have been registered at the US ClinicalTrials.gov [7]. Real-time data is also available with a meta-analysis of 55 studies to date. As per data available on 16 May 2021, 100% of 36 early treatment and prophylaxis studies report positive effects (96% of all 55 studies). Of these, 26 studies show statistically significant improvements in isolation. Random effects meta-analysis with pooled effects using the most serious outcome reported 79% and 85% improvement for early treatment and prophylaxis respectively (RR 0.21 [0.11–0.37] and 0.15 [0.09–0.25]). The results were similar after exclusion based sensitivity analysis: 81% and 87% (RR 0.19 [0.14–0.26] and 0.13 [0.07–0.25]), and after restriction to 29 peer-reviewed studies: 82% and 88% (RR 0.18 [0.11–0.31] and 0.12 [0.05–0.30]). Statistically significant improvements were seen for mortality, ventilation, hospitalization, cases, and viral clearance. 100% of the 17 Randomized Controlled Trials (RCTs) for early treatment and prophylaxis report positive effects, with an estimated improvement of 73% and 83% respectively (RR 0.27 [0.18–0.41] and 0.17 [0.05–0.61]), and 93% of all 28 RCTs. These studies are tabulated in Table 1. The probability that an ineffective treatment generated results as positive for the 55 studies to date is estimated to be 1 in 23 trillion (p = 0.000000000000043). The consistency of positive results across a wide variety of cases has been remarkable. It is extremely unlikely that the observed results could have occurred by chance [8].

Table 1 All 55 ivermectin COVID-19 trials (As per data available on 16 May 2021) divided based on stage of treatment (Early Vs Late) and the type of study

Full size table

However, a controlled outpatient trial by López-Medina et al. demonstrated that, in mild COVID-19, Ivermectin showed no improvement [9]. Misinterpretation of results were noted due to possible gaps in regards to the study quality (study design, the methodology adopted, statistical analysis, and hence the conclusion).

Ivermectin has rapid oral absorption, high liposolubility, is widely distributed in the body, metabolized in the liver (cytochrome P450 system) and excreted almost exclusively in feces [4]. Following a standard oral dose in healthy humans, it reaches peak plasma levels at 3.4 to 5 h; and plasma half-life has been reported to be 12 to 66 h [10]. Despite its widespread use, there are relatively few studies on the pharmacokinetics of Ivermectin in humans [11]. Ivermectin binds strongly to plasma proteins in healthy subjects (93.2%) [12]. Such an "avid binding" can be beneficial when administered in countries where malnutrition and hypoalbuminemia are common, leading to an increased availability of "free fraction" of ivermectin [4]. Hypoalbuminemia is a frequent finding in patients with COVID-19 and it also appears to be linked to the severity of lung injury [13]. Therefore, Ivermectin might be useful when used in such a setting.

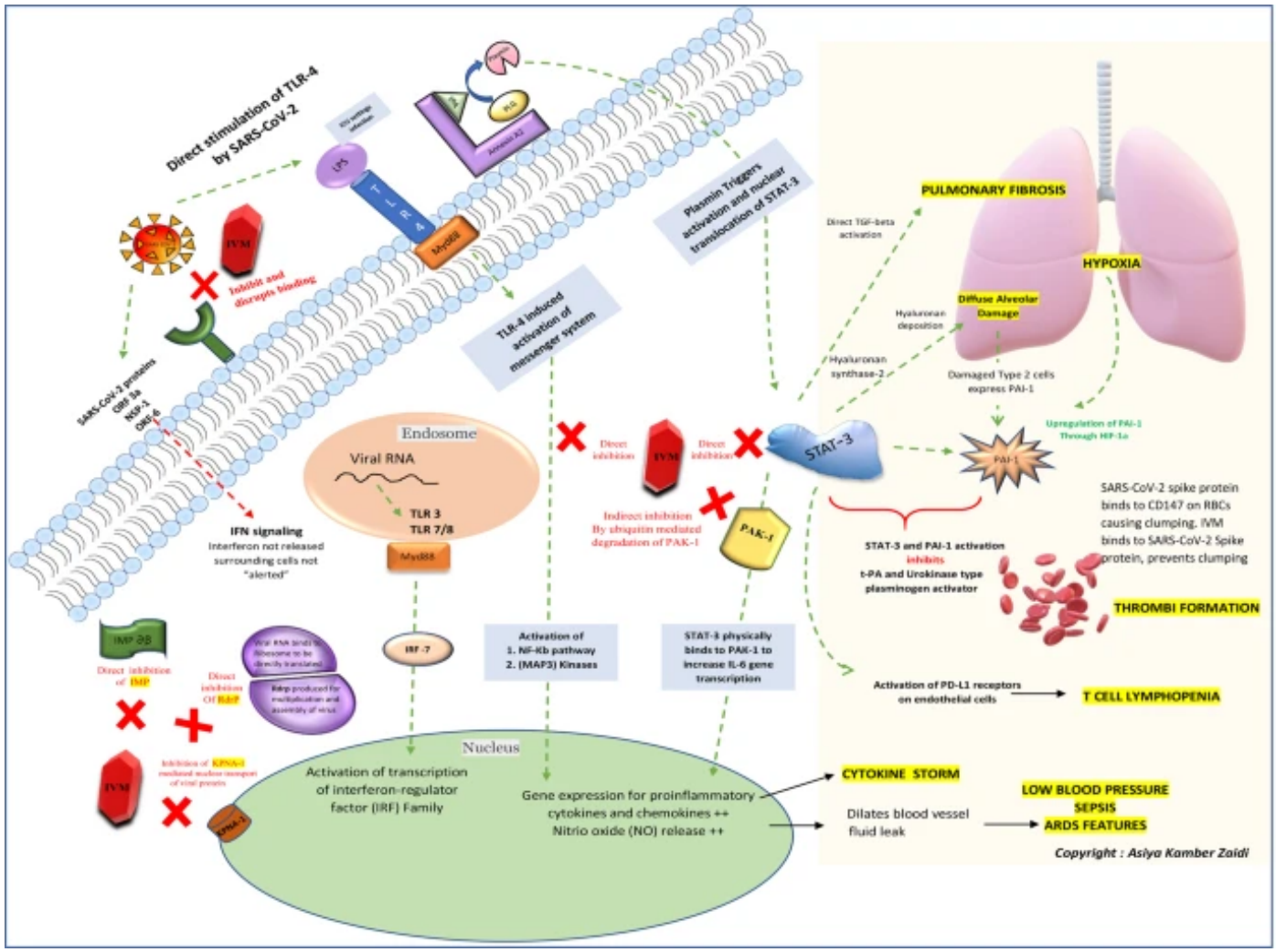
There is evidence supporting the use of Ivermectin in decreasing mortality figures in patients with SARS-CoV-2 infection. However, the use of ivermectin orally in an outpatient setting also requires strict and well defined guidelines to avoid any form of overdosing that could lead to toxicity. A study by Baudou, E et. al described two human ABCB1 nonsense mutations associated with a loss of function in a patient who had an adverse reaction to ivermectin after the administration of a usual dose. This finding warrants caution regarding medical prescriptions of ivermectin and other ABCB1 substrates [14].

This article aims to discuss the mechanism of action by summarizing the in vitro and in vivo evidence demonstrating the role of Ivermectin in COVID-19 as per the available literature over the years. [Table 2] A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications has been proposed. [Fig. 1]

Table 2 A list of studies demonstrating the role of Ivermectin (IVM) on SARS-CoV-2

Full size table

Fig. 1: A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications.



Ivermectin; IVM (red block) inhibits and disrupts binding of the SARS-CoV-2 S protein at the ACE-2 receptors (green). The green dotted lines depict activation pathways and the red dotted lines depict the inhibition pathways. The TLR-4 receptors are directly activated by SARS-CoV-2 and

also by LPS mediated activation (seen during ICU settings) causing activation of NF-Kb pathway and MAP3 Kinases leading to increased intranuclear gene expression for proinflammatory cytokines and chemokines (responsible for cytokine storm) and NO release (responsible for blood vessel dilatation, fluid leak, low blood pressure, ARDS and sepsis). The NF-Kb and STAT-3 pathway activation is central to the pathogenesis and sequelae of COVID-19. STAT-3 physically binds to PAK-1 and increases IL-6 transcription. The annexin A2 at the cell surface converts plasminogen; PLG to plasmin under the presence of t-PA. Plasmin triggers activation and nuclear translocation of STAT-3. An upregulation of STAT-3 stimulates hyaluronan synthase-2 in the lung cells causing hyaluronan deposition leading to diffuse alveolar damage and hypoxia. STAT-3 also directly activates TGF-beta initiating pulmonary fibrosis; a typical characteristic of SARS-COV-2 lung pathology. The damaged type 2 cells express PAI-1 and an already hypoxic state also causes an upregulation of PAI (through Hypoxic inducible factor-1) along with direct stimulation by STAT-3. Simultaneous STAT-3 and PAI-1 activation inhibits t-PA and urokinase-type plasminogen activator leading to thrombi formation. Also, the SARS-CoV-2 spike protein binds to the CD147 on red blood cells and causes clumping. *IVM in turn, binds to SARS-CoV-2 Spike protein and hence prevents clumping*. T cell lymphopenia in COVID-19 can also be attributed to the direct activation of PD-L1 receptors on endothelial cells by STAT-3. *IVM directly inhibits the NF-kb pathway, STAT-3, and indirectly inhibits PAK-1 by increasing its ubiquitin-mediated degradation*. The natural antiviral response of a cell is through interferon regulatory genes and viral RNA mediated activation of TLR-3 and TLR7/8- Myd88 activation of transcription of interferon-regulator (IRF) family. For a virus to establish an infection, this antiviral response needs to be inhibited by blocking interferon production. The proteins such as importin and KPNA mediate nuclear transport of viral protein and subsequent IFN signaling. The SARS-CoV-2 proteins (ORF-3a, NSP-1, and ORF-6) directly block IFN signaling causing the surrounding cells to become unsuspecting victims of the infection. *IVM inhibits both importin a-b (green) as well as the KPNA-1 receptors (brown) causing natural antiviral IFN release. IVM also inhibits viral RdrP, responsible for viral replication*. *IVM* Ivermectin, *ACE-2* angiotensin-converting-enzyme 2, *LPS* Lipopolysaccharide, *TLR* Toll-like receptor, *t-PA* tissue-like plasminogen activator, *PLG* Plasminogen, *IMPab* Importin alpha-beta, *Rdrp* RNA dependant RNA polymerase, *KPNA-1* Karyopherin Subunit Alpha 1, *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells, *Map3Kinases* Mitogen-activated Kinases, *PAK-1* P21 Activated Kinase 1, *STAT-3* Signal transducer and activator of transcription 3, *PAI-1* Plasminogen activator inhibitor-1, *HIF-1* Hypoxia-Inducible Factor

Full size image

Methods

A comprehensive search of the PubMed database was conducted from January 1, 2008 up to January 30, 2021 using syntax constructed using MeSH Database as follows: (stromectol OR Ivermectin OR

"dihydroavermectin") OR (22 AND 23-dihydroavermectin B) AND (antiviral OR virus OR COVID-19 OR SARS-CoV-2). All the results obtained were manually reviewed for content, relevance and included when considered appropriate. The papers cited in the references were also reviewed and included when considered appropriate. The articles were retrieved manually to exclude any duplicates.

Results

Ivermectin as an anti-helminth

Ivermectin has been approved as an anti-helminthic [15]. It is a selective positive allosteric modulator at the glutamate-gated chloride channels found in nematodes and insects and acts by binding to these channels leading to chloride ion influx causing hyperpolarization of the cell and hence, dysfunction [16]. However, at higher concentrations, Ivermectin can also bind to host GABA receptors only when the blood-brain barrier (BBB) is "leaky". This is not the case in healthy human beings with an intact BBB as the drug is "excluded" by a *p*-glycoprotein drug pump (MDR-1). Chandler et al. considered Ivermectin to be free of potential neurological adverse drug reactions, except in situations of overdose [17].

SARS-CoV-2 virus structure

SARS-CoV-2 is a sarbecovirus with structural similarity to SARS-CoV-1. Out of the four structural proteins of the SARS-CoV-2 beta coronavirus, namely: Spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein, the S protein is responsible for eliciting potent neutralizing antibody responses. The entry of SARS-CoV-2 into the host cell is mediated by the binding of the S1 subunit of its S protein (receptor binding domain) to the Angiotensin-converting enzyme 2 (ACE-2) receptors present

on the host cell surface [18]. The S2 subunit is associated with a fusion protein that binds with the cell membrane after priming with Transmembrane protease, serine 2 (TMPRSS-2) and is responsible for fusion with the host cell.

The SARS-CoV-2 genome consists of ~29.8 kb nucleotides; it possesses 14 open reading frames (ORFs) encoding 27 proteins [19]. The 5′ two-thirds of the viral genome encodes the replicase gene. It contains two ORFs: ORF1a and ORF1b. ORF1a/b encodes two polyproteins by polymerase frameshifting; these are then post-translationally cleaved into 15 non-structural proteins (nsps): nsp1–10 and nsp12–16. The rest of the genome encodes for the four structural proteins [(S protein, E protein, M protein, N protein], in addition to eight accessory proteins (3a/3b, p6, 7a/7b, 8b, 9b, and ORF14) [19]. The replicase also encodes the papain-like protease (PLpro) and the serine-type protease or main protease (Mpro) [20].

In principle, a molecule can act as an anti-viral drug if it "inhibits some stage of the virus replication cycle, without being too toxic to the body's cells [21]."

The possible modes of action of anti-viral agents would include the following:

1.

Inactivate extracellular virus particles.

2.

Prevent viral attachment and/or entry.

3.

Prevent replication of the viral genome.

4.

Prevent synthesis of specific viral protein(s).

5.

Prevent assembly or release of new infectious virions

The role of Ivermectin against the SARS-CoV-2 virus

The targets of activity of Ivermectin can be divided into the following four groups:

A.

Direct action on SARS-CoV-2

Level 1: Action on SARS-CoV-2 cell entry

Level 2: Action on Importin (IMP) superfamily

Level 3: Action as an Ionophore

B.

Action on host targets important for viral replication

Level 4: Action as an antiviral

Level 5: Action on viral replication and assembly

Level 6: Action on post-translational processing of viral polyproteins

Level 7: Action on Karyopherin (KPNA/KPNB) receptors

C.

Action on host targets important for inflammation

Level 8: Action on Interferon (INF) levels

Level 9: Action on Toll- like-Receptors (TLRs)

Level 10: Action on Nuclear Factor-κB (NF-κB) pathway

Level 11: Action on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae

Level 12: Action on P21 activated Kinase 1 (PAK-1)

Level 13: Action on Interleukin-6 (IL-6) levels

Level 14: Action on allosteric modulation of P2X4 receptor

Level 15: Action on high mobility group box 1 (HMGB1),

Level 16: Action as an immunomodulator on Lung tissue and olfaction

Level 17: Action as an anti-inflammatory

D.

Action on other host targets

Level 18: Action on Plasmin and Annexin A2

Level 19: Action on CD147 on the RBC

Level 20: Action on mitochondrial ATP under hypoxia on cardiac function

The direct “antiviral targets” may be useful in the early stages while the anti-

inflammatory targets might be addressed in the later stages of the disease.

Direct action of Ivermectin on SARS-CoV-2

Level 1: Action on SARS-CoV-2 cell entry

A study by Lehrer S et al observed that Ivermectin docked in the region of leucine 91 of the SARS-CoV-2 spike protein and histidine 378 of the host cell ACE-2 receptor blocking its entry into the host cell [22]. In yet another study by Eweas et al., potential repurposed drugs such as Ivermectin, chloroquine, hydroxychloroquine, remdesivir, and favipiravir were screened and molecular docking with different SARS-CoV-2 target proteins including S and M proteins, RNA-dependent RNA polymerase (RdRp), nucleoproteins, viral proteases, and nsp14, was performed. Ivermectin showed the following 5 important docking properties [23]:

1.

Highest binding affinity to the predicted active site of the S glycoprotein (Mol Dock score –140.584) and protein–ligand interactions (MolDock score–139.371).

2.

Considerable binding affinity to the predicted active site of the SARS-CoV-2 RdRp protein (MolDock score –149.9900) and protein–ligand interactions (MolDock score –147.608), it formed H-bonds with only two amino acids: Cys622 and Asp760.

3.

Highest binding affinity (MolDock score –212.265) to the predicted active site of nsp14.

4.

The highest binding affinity to the active site of the TMPRSS2 protein (MolDock score –174.971) and protein–ligand interactions (MolDock score –180.548). Moreover, it formed five H-bonds with Cys297, Glu299, Gln438, Gly462, and Gly464 amino acid residues present at the predicted active site of the TMPRSS protein

5.

The free binding energy of the spike protein (open) was higher in Ivermectin (–398.536 kJ/mol) than remdesivir (–232.973 kJ/mol).

An In-silico data analysis conducted by Choudhury et al. demonstrated that Ivermectin efficiently utilizes viral spike protein, main protease, replicase, and human TMPRSS2 receptors as the most possible targets for executing its "antiviral efficiency" by disrupting binding. Since Ivermectin exploits protein targets from both, the virus and human, this could be the behind its excellent in vitro efficacy against SARS-CoV-2 [24].

The development of vaccines for SARS-CoV-2 is centered around spike protein biology (virus targeted) and the recently documented "vaccine escape strains" have been a cause of worry. In such a situation, Ivermectin, is both, virus as well as host targeted and hence could act as a potential therapeutic against these new strains that could "escape" immunity offered by the vaccine.

Level 2: Action on Importin (IMP) superfamily

Inside the cell, the nuclear transport of proteins into and out of the nucleus is signal-dependent and mediated by the Importin (IMP) superfamily of proteins that exist in α and β forms. This IMPα/β1 exists as a heterodimer

with a "IBB" (IMP β-binding) site present over IMP α that binds to IMP β1 on "cargo recognition" by IMPα. The SARS-CoV-2 virus upon host cell entry tends to "load" its proteins over the host protein IMP α/β1 heterodimer (importin) to enter the nucleus through the nuclear pore complex. Once inside, the importin molecule detaches while the viral protein from the SARS-CoV-2 virus hijacks the host cell machinery and inhibits the natural cell "anti-viral" response by blocking the release of interferon (an antiviral substance released by an infected cell to alert the surrounding cells of an ongoing viral attack). As a result, the surrounding cells become "unsuspecting victims" of the virus and the infection continues with the virus escaping recognition by the immune cells [25]. Ivermectin, in presence of a viral infection, targets the IMPα component of the IMP α/β1 heterodimer and binds to it, preventing interaction with IMP β1, subsequently blocking the nuclear transport of viral proteins. This allows the cell to carry out its normal antiviral response [26]. In such a case, it should be noted that the activity of Ivermectin here is viro-static, that is, it neutralizes the virus by competing for the same receptor.

Level 3: Action as an Ionophore

Ionophores are molecules that typically have a hydrophilic pocket which constitutes a specific binding site for one or more ions (usually cations), while its external surface is hydrophobic, allowing the complex thus formed to cross the cell membranes, affecting the hydro-electrolyte balance [27]. It can be hypothesized that two ivermectin molecules, reacting with each other in a "head-tail" mode, can create a complex suitable to be considered such [28]. These ionophores allow neutralizing the virus at an early stage of the infection before it can adhere to the host cells and enter it to exploit their biochemical machinery for the production of other viral particles.

Action on host targets for viral replication

Level 4: Action as an antiviral

A systematic review article by Heidary, F. discussed the "anti-viral" properties of Ivermectin against other viruses including the RNA viruses such as Zika Virus (ZKV), Dengue virus, yellow fever virus (YFV), and West Nile virus (WNV), Hendra virus (HEV), Newcastle virus, Venezuelan equine encephalitis virus (VEEV), Chikungunya virus (CHIKV), Semliki Forest virus (SFV), and Sindbis virus (SINV), Avian influenza A virus, Porcine Reproductive and Respiratory Syndrome virus (PRRSV), Human immunodeficiency virus type 1 as well as DNA viruses such as Equine herpesvirus type 1 (EHV-1) and Pseudorabies virus (PRV) [29].

Level 5: Action on viral replication and assembly

An in-vitro study by Caly L et al. demonstrated that the Vero/hSLAM cells infected with the SARS-CoV-2 virus when "exposed" to 5 µM Ivermectin showed a 5000-fold reduction in viral RNA at 48 h when compared to the control group [30]. This study attracted opinions regarding the inability of Ivermectin to achieve the therapeutic effect of COVID-19 through routine dosage. Contrary to this, Arshad et al, by utilizing modeling approach, predicted lung accumulation of Ivermectin over 10 times higher than EC_{50}. This likelihood of attainment of higher lung tissue concentrations of Ivermectin leaves the door open for further research especially for respiratory infections [31].

An explanation for the study by Caly et al was provided in a review article: Global trends in clinical studies of ivermectin in COVID-19 by Yagisawa et al., co-authored by Prof. Satoshi Ōmura, regarding the "setting of the sensitivity for experimental systems in vitro". As per the authors, using Vero/hSLAM cells, the antiviral activity of the test drug was reliably measured and the sensitivity of the $IC_{50} = 2$ µM set by them was appropriate as neither false

positives nor false negatives occurred. Therefore, the study by Caly et al. merely indicated that ivermectin was found to have anti-SARS-CoV-2 activity in vitro—no more, no less. Also, the fact that there are in vivo infection experiments that could be used to connect in vitro experiments to clinical studies [32].

Another in-silico study by Swargiary et al. demonstrated the best binding interaction of −9.7 kcal/mol between Ivermectin and RdRp suggesting inhibition of viral replication [33]. The RdRP residing in nsp12 is the centerpiece of the coronavirus replication and transcription complex and has been suggested as a promising drug target as it is a crucial enzyme in the virus life cycle both for replication of the viral genome but also for transcription of subgenomic mRNAs (sgRNAs) [34]. Ivermectin binds to the viral rdrp and disrupts it. The highly efficient binding of ivermectin to nsp14 confirms its role in inhibiting viral replication and assembly. It is well known that nsp14 is essential in transcription and replication. It acts as a proofreading exoribonuclease and plays a role in viral RNA capping by its methyltransferase activity [35]. Moreover, highly efficient binding of ivermectin to the viral N phosphoprotein and M protein is suggestive of its role in inhibiting viral replication and assembly [23].

Level 6: Action on post-translational processing of viral polyproteins

Once gaining entry into the host cell, the viral RNA is translated by the host ribosome into a large “polyprotein”. Some enzymes break away through autoproteolysis from this polyprotein and further help other proteins to break off and carry out their function for replication. One such enzyme, 3 chymotrypsin-like proteases (3′cl pro/ Mpro) is responsible for working on this polyprotein causing other proteins to “librate” and carry out viral replication. Ivermectin binds to this enzyme and disrupts it. It also efficiently binds to both proteins, Mpro, and to a lesser extent to PLpro of SARS-CoV-2;

therefore, it has a role in preventing the post-translational processing of viral polyproteins [23].

Level 7: Action on Karyopherin (KPNA/KPNB) receptors

Karyopherin-α1 (KPNA1) is essential for the nuclear transport of signal transducers and activators of transcription 1 (STAT1) [36], and the interaction between STAT1 and KPNA1 (STAT1/KPNA1) involves a nonclassical nuclear localization signal (NLS). Ivermectin inhibits the KPNA/KPNB1- mediated nuclear import of viral proteins allowing the cell to carry out its normal antiviral response [30].

Action on host targets for inflammation

Level 8: Action on Interferon (INF) levels

These virus-infected cells release interferons that bind to the IFN receptors present on neighboring cells alerting them of a viral attack. The IFN-I and IFN-III receptors then further activate members of the JAK-STAT family. The virus after gaining entry into the host cell hijacks the host cell machinery and works towards antagonizing the normal interferon-mediated host cell antiviral response. SARS-CoV-2 proteins such as ORF3a, NSP1, and ORF6 inhibit IFN-I signaling [37, 38]. As a result, the cells surrounding the SARS-CoV-2 virus-infected cell "fail" to receive "critical and protective IFN signals" causing this SARS-CoV-2 virus to replicate and spread without any hindrance. This is one of the main reasons that, at this stage, COVID-19 infection is "hard to detect" clinically [39].

Ivermectin has been shown to promote the expression of several IFN-related genes, such as IFIT1, IFIT2, IF144, ISG20, IRF9, and OASL [40].

Level 9: Action on Toll- like-Receptors (TLRs)

Upon virus entry, the intracellular pattern recognition receptors (PRRs) present on the host cells are responsible for detecting the viral attack. The virus activates one such PRR named the Toll-like receptors (TLRs). These receptors are present on various immune system cells that help them locate and bind with the pathogen. The activation of TLRs, causes oligomerization, further activating downstream interferon regulatory factors (IRFs) and nuclear factor-kappa B (NF-kB) transcription factors inducing INF production [41]. Ivermectin plays a role in the blockade of activation of NF-kB pathway and inhibition of TLR4 signaling [42].

Level 10: Action on Nuclear Factor-κB (NF-κB) pathway

Activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines [43]. Jiang et al. demonstrated that Ivermectin at its very low dose, which did not induce cytotoxicity, drastically reversed the resistance of tumor cells to the chemotherapeutic drugs both in vitro and in vivo by inhibition of the transcriptional factor NF-κB [44]. Also, Zhang et al., suggested that Ivermectin inhibits lipopolysaccharide (LPS)-induced production of inflammatory cytokines by blocking the NF-κB pathway and improving LPS-induced survival in mice [42]. Therefore, using Ivermectin would be helpful in ICU settings where there are increased chances of bacterial infections (LPS mediated).

Level 11: Action on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae

A strong correlation exists between SARS-CoV-2 viral load, disease severity, and progression [45]. COVID-19 not only causes flu-like symptoms such as fever, dry cough but could also lead to widespread thrombosis with microangiopathy in pulmonary vessels [46], raise D-dimer levels [47], cause

lymphopenia [48], raise proinflammatory cytokine and chemokine production [49] as well as lead to a significant elevation of CRP levels [50]. SARS-CoV-2 has structural similarity with SARS-CoV-1. Several SARS-CoV-1 proteins antagonize the antiviral activities of IFNs and the downstream JAK (Janus kinase)-STAT signaling pathways they activate. JAK family kinases display a wide range of functions in ontogeny, immunity, chronic inflammation, fibrosis, and cancer [51].

The host proteins, such as the members of the signal transducers and activators of transcription (STATs) and NF-κB, enter the nucleus through nuclear envelope-embedded nuclear pores mediated by the IMPα/β1 heterodimer and play a role in COVID-19 pathogenesis. Frieman et al. demonstrated that accessory SARS ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane [52]. A review article by Matsuyama et al, hinted at SARS-CoV-2-mediated inhibition of IFN and STAT 1, with the subsequent shift to a STAT 3 dominant signaling network that could result in almost all of the clinical features of COVID-19 [39].

Before discussing further, it is important to understand the link between STAT-3 upregulation and COVID-19 sequelae and the role of Ivermectin in inhibiting STAT-3. STAT-3 acts as a “central hub” that mediates the detrimental COVID-19 cascade. In the lungs, STAT-3 activates Hyaluronan synthase-2 leading to deposition of hyaluronan causing diffuse alveolar damage. The damaged type 2 alveolar cells express PAI-1 (plasminogen activator inhibitor-1). Additionally, hypoxia due to diffuse alveolar damage causes an upregulation of PAI-1 through HIF-1a. STAT-3 also directly activates PAI-1. The simultaneous activation of PAI-1 and STAT-3 inhibits t-PA and urokinase-type plasminogen activator leading to thrombi formation in the capillaries. PAI-1 also binds to TLR-4 receptors on macrophages further activating the NF-kB pathway.

The “cytokine storm” typical of severe COVID-19 involves STAT-3 mediated upregulation of proinflammatory cytokines, TNFα, and IL-6 in macrophages. Additionally, STAT-3 induces a C-reactive protein that upregulates PAI-1 levels. STAT-3 is directly responsible for activating IL-6 gene transcription which further leads to an increase in TGF-β causing pulmonary fibrosis. The PD-L1 receptors present on the endothelial cells are activated by STAT-3 causing T cell lymphopenia. Ivermectin inhibits STAT-3 through direct inhibition preventing COVID-19 sequalae [39].

Level 12: Action on P21 activated Kinase 1 (PAK-1)

The p21 activated kinase 1 (PAK1) physically binds to both JAK1 and STAT3, and the resultant PAK1/STAT3 complex activates IL-6 gene transcription responsible for cytokine storm in COVID-19 [53]. Ivermectin suppresses the Akt/mTOR signaling and promotes ubiquitin-mediated degradation of PAK-1 hence compromising STAT-3 activity and decreasing IL-6 production [54].

Level 13: Action on Interleukin-6 (IL-6) levels

A study by Zhang et al. demonstrated that Ivermectin suppressed IL-6 and TNFα production, two major components of the detrimental cytokine storm induced by SARS-CoV-2 and “dramatically reduced” IL-6/IL-10 ratio modulating infection outcomes [42, 55].

Level 14: Action on allosteric modulation of P2X4 receptor

P2X receptors are the channels selective to cation, are gated by extracellular ATP [56] and mediate several functions in health and disease [57]. From the seven subunits of P2X receptors, $P2X_4$ is most sensitive to Ivermectin. Positive allosteric modulation of $P2X_4$ by Ivermectin enhances ATP-mediated secretion of CXCL5 (pro-inflammatory chemokine). CXCL5 is a chemo-attractant molecule expressed in inflammatory cells in different

tissues and modulates neutrophil chemotaxis and chemokine scavenging [58].

Level 15: Action on high mobility group box 1 (HMGB1)

The damage-associated molecular pattern high mobility group box 1 (HMGB1), is released by damaged cells acting as an agonist for the TLR4 receptor and hence mediating lung inflammation associated with COVID-19 [59]. Ivermectin inhibits HMGB1 [60].

Level 16: Action as an immunomodulator on Lung tissue and olfaction

In a study by DeMelo et al., the effects of Ivermectin were investigated on SARS-CoV-2 infection using the golden Syrian hamster as a model for COVID-19. Both, male and female adult golden Syrian hamsters were intranasally inoculated with 6×10^4 PFU of SARS-CoV-2. At the time of infection, animals received a single subcutaneous injection of Ivermectin (antiparasitic dose of 400 µg/kg) classically used in a clinical setting and were monitored over four days. Mock-infected animals received the physiological solution only. Interestingly, Ivermectin had a sex-dependent and compartmentalized immunomodulatory effect, preventing clinical deterioration and reducing the olfactory deficit in infected animals. This effect was sex-dependent: infected males presented a reduction in the clinical score whereas a complete absence of signs was noticed in the infected females. Regarding the olfactory performance, 83.3% (10/12) of the saline-treated males presented with hyposmia/anosmia, in contrast to only 33.3% (4/12) of IVM-treated males (Fisher's exact test $p = 0.036$). No olfactory deficit was observed in IVM-treated females (0/6), while 33.3% (2/6) of saline-treated females presented with hyposmia/anosmia (Fisher's exact test $p = 0.455$). Ivermectin dramatically reduced the IL-6/IL-10 ratio in lung tissue, which likely accounts for the more favorable clinical presentation

in treated animals [55]. Loss of smell has been reported as one of the common symptoms in COVID-19 [61]. Interestingly, majority of patients in India regained their sense of smell after a brief anosmic period during their clinical course. Ivermectin is being used in India as one of the first-line drugs for COVID-19 treatment. It could be hypothesized that Ivermectin might have a role to play in reducing SARS-CoV-2 induced olfactory deficit.

Level 17: Action as an anti-inflammatory

The mechanism for anti-inflammatory action of Ivermectin was explained as inhibition of cytokine production by lipopolysaccharide challenged macrophages, blockade of activation of NF-kB, and the stress-activated MAP kinases JNK and p38, and inhibition of TLR4 signaling [42, 61, 62]. Moreover, Immune cell recruitment, cytokine production in bronchoalveolar lavage fluid, IgE, and IgG1 secretion in serum as well as hyper-secretion of mucus by goblet cells was reduced significantly by Ivermectin [63].

Action on other host targets

Level 18: Action on Plasmin and Annexin A2

As per study by Kamber Zaidi et al, annexin A2 may be linked to COVID-19 pathophysiology. Annexin A2 acts as a co-receptor for the conversion of plasminogen to plasmin in the presence of t-PA. Increased plasmin levels are found in co-morbid states and is also responsible for early stages of viral infection. Plasmin leads to direct activation of STAT-3 inducing detrimental COVID-19 sequelae. Ivermectin directly inhibits STAT-3 and could play a role in the inhibition of COVID-19 complications.

Level 19: Action on CD147 on the RBC

The transmembrane receptor CD147, present on the red blood cell (RBC)

along with ACE-2 has been recognized as a key binding site for SARS-CoV-2 spike protein. The SARS-CoV-2 does not internalize into the RBC but such attachments can lead to clumping [65]. Ivermectin binds to the S protein of the virus making it unavailable to bind with CD147. This action might also be beneficial in advanced stages of COVID-19 presenting with clotting/thrombotic phenomena.

Level 20: Action on mitochondrial ATP under hypoxia on cardiac function

SARS-CoV-2 has been a well-known cause for acute myocardial injury and chronic damage to the cardiovascular system in active infection as well as in long haulers [66]. Nagai et al. demonstrated that Ivermectin increased mitochondrial ATP production by inducing Cox6a2 expression and maintains mitochondrial ATP under hypoxic conditions preventing pathological hypertrophy and improving cardiac function [67].

Conclusion

Considering the urgency of the ongoing COVID-19 pandemic, simultaneous detection of various new mutant strains and future potential re-emergence of novel coronaviruses, repurposing of approved drugs such as Ivermectin could be worthy of attention.

Change history

22 June 2021

Editor's Note: Readers are alerted that the conclusions of this paper are subject to criticisms that are being considered by the editors and the publisher. A further editorial response will follow the resolution of these issues.

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Acknowledgements

We would like to thank all the academicians, physicians, and scientists

dedicating their efforts and time to COVID-19 research. A special thank you to children who bring positivity and hope in these difficult times, especially Ginevra Dehgani.

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Ethics declarations

Conflict of interest

The authors declare no competing interest.

Additional information

About this article

Cite this article

Zaidi, A.K., Dehgani-Mobaraki, P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. *J Antibiot* (2021). https://doi.org/10.1038/s41429-021-00430-5

Download citation

Received11 May 2021

Revised17 May 2021

Accepted20 May 2021

Published15 June 2021

DOIhttps://doi.org/10.1038/s41429-021-00430-5

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