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Prospective mode of action of Ivermectin: SARS-CoV-2

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ABSTRACT

The well-known anti-helminthic drug ivermectin (IVM) has been established as an example of drug repurposing for the management of SARS-CoV-2 infection. Various study has been done to understand the inhibitory mechanism of IVM against SARS-CoV-2 targets. Broadly, IVM has been categorized as a host-directed agent and the proposed mechanism involves inhibition of the IMPα1/IMPβ-mediated nuclear import of viral proteins. In addition, in vitro/in vivo and molecular docking/dynamic simulation studies suggested multitargets mechanism of IVM against SARS-CoV-2. Present manuscript attempts to provide an overview of the detailed mechanism of action based on experimental and computational studies. The knowledge of binding interaction of IVM and SARS-CoV-2 targets will give the direction to developed new and potential anti-COVID agents.

1. Introduction

The well-known anti-helminthic drug ivermectin (IVM) was introduced in late 1970s [1]. Few years after its approval for use in animals, it was approved for clinical use in human and received a Nobel Prize (Physiology/Medicine) in 2015 [1–3]. Initially it was named as avermectin. Naturally occurring avermectins consists of four analogs, avermectin A1, A2, B1, and B2, each of exist as two variants, a and b. During the progress and synthetic derivatization, it focused as 22,23-dihydroavermectin. Chemical structure of IVM consists of homologues mixture of 5-O-dimethyl-22,23-dihydroavermectin B1a (80%) and B1b (20%) [4]. IVM have been reported for high lipid solubility and broad-spectrum of activity [1–3]. It has been investigated for biological activity on parasites, nematodes, arthropods, flavivirus, mycobacteria, and mammals. IVM has been reported for its multiple mechanisms such as antiparasitic, antiviral and host immunomodulatory properties. In cancer cell, IVM could show antiproliferative action and glucose and cholesterol regulator in animals [5]. It may possess some secondary toxic effects on cells (see Fig. 1).

The broad antiviral spectrum for IVM has been explored by using experimental and theoretical studies against RNA and DNA viruses (Fig. 2). Some of the RNA viruses for which the antiviral profile of IVM has been investigated includes Dengue virus, Yellow fever virus, West Nile virus, Hendra virus (10 μM), Newcastle virus (100 μg/ml), Venezuelan equine encephalitis virus (1 μM), Chikungunya virus, Semiliki Forest virus, Sindbis virus, Avian influenza A virus (10 μM), Porcine Reproductive and Respiratory Syndrome virus (1–15 μM), and Human immunomodulatory virus type 1 (IC50 = 4.8 μM). IVM has exhibited inhibitory profile against DNA viruses namely, Equine herpesvirus type 1, Pseudorabies virus (1.5 or 2.5 μM, delayed proliferation and no inhibition of virus adsorption in cells), BK polyomavirus, Porcine circovirus 2 (concentrations = 50 or 100 μg/ml, no cytotoxicity & reduced viral load by 41% and 28.2%), and Bovine herpesvirus 1 virus (IVM concentration = 25 μM) [6]. In case of DENV, during phase III (2014–2017) trials IVM was found to be safe (single daily oral dose) and has reduced the levels of viral NS1 protein. But it failed to produce any change in viremia [7]. The viral replication inhibitory properties of IVM in SARS-CoV-2 have been evaluated using TaqMan Real-Time RT-PCR assay resulting into IC50 of ~0.2 μM [8].

2. Mechanism of action for IVM

The efficacy of IVM in the treatment of broad spectrum of parasitic infections as well as other viruses and bacteria is well established, but the mode of action is less clear (Table 1) [9]. IVM at nanomolar concentrations affects nematode motility, feeding, and reproduction and acts via ligand-gated chloride channels, specifically those gated by glutamate [9]. In vertebrates the absence of Glutamate-gated chloride channels (GluCls) confers the broad safety margin of IVM. When administered at micro-molar concentrations, IVM can interact with a wider range of
ligand-gated channels found in both invertebrates and vertebrates, including GABA, glycine, histamine, and nicotinic acetylcholine receptors [10].

In recent years efforts have been put to investigate the anti-viral mechanism of IVM against a broad range of viruses including RNA viruses (human immunodeficiency virus-1 (HIV-1), dengue virus (DENV), West Nile virus, Venezuelan equine encephalitic virus (VEEV), influenza, pseudorabies virus (PRV), Zika virus (ZIKV) and the recent coronavirus SARS-CoV-2 [11–17].

Taken together the reported studies, the anti-viral mechanism of IVM against SARS-CoV-2, the RNA virus the proposed mechanism involves inhibition of the IMPα/ß1-mediated nuclear import of viral proteins. Importins are a type of karyopherins, soluble transport receptors involved in nucleo-cytoplasmic transit of the various substrates [8, 18–20]. IMPα/ß1 binds to the coronavirus cargo protein in the cytoplasm and translocates it through the nuclear pore complex (NPC) into the nucleus where the complex falls apart and the viral cargo can reduce the host cell’s antiviral response, leading to enhanced infection. IVM binds to and destabilizes the IMPα/ß1 heterodimer thus prevents IMPα/ß1 from binding to the viral protein and prevents its entry into the nucleus. This results in reduced inhibition of the antiviral responses and thus normal and more efficient antiviral response. Based on this conjecture and the reported in vitro studies it can be assumed that IVM has role in eliminating SARS-CoV-2 [21,22].

IVM can be categorized as a host-directed agent (HDA) as in mammalian cells IVM targets a host protein important for intracellular transport irrespective of the viral component [22]. Use of IVM as a HAD can reduce the viral load through inhibition of key cellular processes in host cells which are controlled by virus to enhance infection and thus suppress the host antiviral response. Use of IVM as HAD even at low concentration in the early stage of infection can enable the body’s immune system for antiviral response before the infections takes control. A schematic presentation explaining the antiviral mechanism against SARS-CoV-2 is provided in Fig. 3.

3. SARS-COV-2 targets for binding of IVM

The very well reported targets for IVM includes glycine receptor subunit α-3 acting as a transmitter-gated ion channel activator and γ-amino butyric acid receptor subunit β-3 which controls GABA-gated chloride ion channel activity [23,24]. For SARS-CoV-2 inhibitory potential, various potential targets are under investigation. In addition to in vivo/in vitro studies, in silico studies of IVM have been reported for following SARS-CoV-2 targets [25].

1. SARS-CoV-2 Spike receptor binding domain attached to ACE2 [26].
2. 3CL protease and HR2 domain [27].
3. SARS-CoV-2 helicase [28].
4. SARS-CoV-2 S-protein [29].

The hypothesized molecular target for Ivermectin i.e., Importin-α has functional diversity and acts as a multifunctional protein like spindle assembly, lamin polymerization, nuclear envelope formation, protein degradation, mRNA-related function, cell surface function, gene expression and cytoplasmic retention [29]. Adaptor proteins bind the nuclear

Table 1

| Species/systems | Target | Effect |
|-----------------|--------|--------|
| Mammals         | Faesson X receptor, WNT-TCF pathway, RNA helicase, tubulin | Glucose, cholesterol and bile homeostasis, cancer chemotherapy, immune-modulation |
| Nematodes       | Ligand-gated chloride channels | Inhibition of feeding, motility, reproduction and host immune-modulation |
| Arthropods      | Ligand-gated chloride channels | Inhibition of feeding, motility, reproduction, interruption of vector-borne disease transmission |
| Flaviviruses    | Viral RNA helicase | Inhibition of replication |

Fig. 1. Chemical structure of Ivermectin.

Fig. 2. Antiviral spectrum of activity for IVM.

Fig. 3. Antiviral mechanism of action for IVM against SARS-CoV-2.
localization sequence (NLS) of import cargoes while recruiting importin β via an N-terminal importin β binding (IBB) domain. The use of adaptors greatly expands and amplifies the repertoire of cellular cargoes that importin β can efficiently import into the cell nucleus and allows for fine regulation of nuclear import [30]. It is proposed that, in addition to cellular factors, certain viral proteins may have developed IBB-like domain to efficiently enter the cell nucleus of infected cells [16].

### Table 2
Molecular docking/dynamic simulation study of IVM with different SARS-CoV-2 protein targets.

| S.N. | Targets                      | PDB          | Docking software | MD Simulation Software and time | IVM binding interaction residues | Docking/MDS interpretation                        | Ref. |
|------|------------------------------|--------------|------------------|--------------------------------|----------------------------------|------------------------------------------|------|
| 1    | Main Protease                | 6LU7/6Y2E/ 6Y2F | AutoDock/MVD 6.0 Desmond (blind docking) | (100ns)/Gromacs (30ns) | Gln189, Pro168, Met165, Pro168, Met49, Leu50, His41/Arg153, Am203/Glu19, Thr25, G1u57, Leu50/Arg4, Lys5, Lys282, Ser284 | Strong and stable binding interactions/IVM B1a binds with a good affinity than IVM B1b | [41, 42, 33, 47] |
| 2    | Papain-like protease         | 6WU1/6W9C    | AutoDock/MVD 6.0 Desmond (100ns)/Gromacs (30ns) | Tyr264, Tyr268, Pro248, Met208, Pro247/Thr74, Arg128 | Ser549, Lys551, Lys621, Pro620, Lys798 | Moderate affinity                         | [41, 42] |
| 3    | RdRp (RTP site)              | 7BV2         | AutoDock/MVD 6.0 Desmond (100ns)/Gromacs (30ns) | Lys545, Ala688, Gln573, Val557, Leu576, Lys577 | Lys545, Ala688, Gln573, Val557, Leu576, Lys577 | Minimum affinity                         | [41] |
| 4    | RdRp (RNA site)              | 7BV2         | AutoDock/MVD 6.0 Desmond (100ns) | Lys545, Ala688, Gln573, Val557, Leu576, Lys577 | Moderate affinity                         | [41] |
| 5    | Helicase (Nsp13; ADP site)   | 6JYT         | AutoDock/MVD 6.0 Desmond (100ns) | Gln537, Ala312, Ser539, Ala313, Glu540, Ala316, Lys520 | Moderate affinity                         | [41] |
| 6    | Helicase (Nsp13; NCB site)   | 6JYT         | AutoDock/MVD 6.0 Desmond (100ns) | Arg212, Arg178, Arg339 Ala312, Cys509, Met378 | Arg212, Arg178, Arg339 Ala312, Cys509, Met378 | Moderate affinity                         | [41] |
| 7    | Npl4 (ExoN)                  | 5CBS         | AutoDock/MVD 6.0 Desmond (100ns) | Gln145, Ala187, Pro141, Pro42 His95, Phe146, Trp186, Phe190 | Moderate affinity                         | [41] |
| 8    | Npl4 (N7-MTase)              | 5CBS         | AutoDock/MVD 6.0 Desmond (100ns) | Ala207, Arg310, Cys340, Pro342, Pro335, Lys336, Trp292, His314 | Strong and stable hydrophobic/hydrophilic binding interactions | [41] |
| 9    | Spike RBD                    | 6MOU/6M17    | AutoDock/MVD 6.0 Desmond (100ns) | Leu545, Gln493, Ser494, G1u484, Tyr449, Phe456, Tyr505, Thr500, Asn501, Tyr505 Moderately affinity/highly Stable during simulation | Moderate affinity/highly Stable during simulation | [41] |
| 10   | Spike monomer (clone)        | 6VXX         | AutoDock/MVD 6.0 Desmond (100ns)/Gromacs (30ns) | Arg803, Val530, Pro507/Thr307, G1u390, Ile3,12, Ala8 | Moderate affinity                         | [41, 42] |
| 11   | Spike trimer (open)          | 6VYB         | AutoDock/MVD 6.0 Desmond (100ns) | Arg803, Val530, Pro507/Thr307, G1u390, Ile3,12, Ala8 | Moderate affinity                         | [41, 42] |
| 12   | S2 (post fusion state)       | 6LXT/6LXH    | AutoDock/MVD 6.0 Desmond (100ns) | Ala50, Arg52/Arg69, Tyr124, Arg127, Glu137/Gln160, Leu161, G1y164, Thr166 | Moderate affinity/highly Stable during simulation | [41, 42, 43] |
| 13   | N protein (C domain)         | 6YUN         | AutoDock/MVD 6.0 Desmond (100ns) | Ala50, Arg52/Arg69, Tyr124, Arg127, Glu137/Gln160, Leu161, G1y164, Thr166 | Moderate affinity/highly Stable during simulation | [41, 42, 43] |
| 14   | N protein (N domain)         | 6YD/6XSM/6YVO | AutoDock/MVD 6.0 Desmond (100ns)/Gromacs (30ns) | Ala50, Arg52/Arg69, Tyr124, Arg127, Glu137/Gln160, Leu161, G1y164, Thr166 | Moderate affinity/highly Stable during simulation | [41, 42, 43] |
| 15   | Nsp9                         | 6WXD         | AutoDock/MVD 6.0 Desmond (100ns) | Ala50, Arg52/Arg69, Tyr124, Arg127, Glu137/Gln160, Leu161, G1y164, Thr166 | Moderate affinity/highly Stable during simulation | [41, 42, 43] |
| 16   | Nsp7, Npl8, Npl12 and Nsp13 | 6XEZ/67MI    | AutoDock/MVD 6.0 Desmond (100ns) | Ala50, Arg52/Arg69, Tyr124, Arg127, Glu137/Gln160, Leu161, G1y164, Thr166 | Moderate affinity/highly Stable during simulation | [41, 42, 43] |
| 17   | M Protein                    | Homology model | MVD 6.0 Gromacs (30ns) | Trp31, Ala8 | Moderate affinity                         | [11] |
COVID-19 [34]. Various in silico approaches utilized to find out the binding mechanism of IVM and covid 19 drug targets [35,36]. Among these approaches, Molecular dynamics (MD) simulation is a powerful computational approach for study of conformational flexibility of water molecules, salt and entropy factors on the forces of binding interactions drug and targets. It gives virtual motion picture (video) of drug and targets interaction [37]. To promote research on covid 19 drug development, Shaw and group released the long run MD simulation trajectory and their videos of COVID-19 targets [38]. The critical analysis of the released MD simulation trajectory at atomic level will be a big leap in the design and discovery of anti-covid drugs.

COVID-19 is an enveloped, positive-sense, single-stranded RNA betacoronavirus consist of number of targets [39]. The IVM virtually explored against different targets to find out its binding interaction mechanism [40-45]. These targets are main proteases (Mpro/3CLpro), papain-like protease, RNA-dependent RNA polymerase (RdRp: RTP site/RNA site), Helicase (Nsp13; NCB/ADP site), Nsp14 (ExcN), Nsp14 (N7-MTase), nonstructural protein (Nsp9), RdRp components (nsp7, nsp8, nsp12), receptor binding domain (RBD) of the surface spike (S)/SRBD, Spike monomer (close), Spike trimer (open), S2 (post fusion state), Membrane (M) protein and C/N domains of Nucleocapsid (N) protein [41-45].

Several groups performed 100 ns MD simulation of docked complex of IVM and COVID-19 reported targets to comprehend the binding energy scenarios with aim of therapeutic drug development. Among these, IVM showed highest affinity and stability with Nsp9 (PDB: 6WXD) and Spike RBD (PDB: 6M0J) during simulation experiment [41,45]. The binding interaction stability of IVM-Nsp9 (Fig. 4) and IVM -Spike RBD docked complex confirmed by RMSD and RMFS plots [40,43]. Initially binding interaction validated by binding energy generated by docking experiment and further stability of docked model confirmed by MD simulation. The binding free energy (ΔGbind = −84.85 kcal/mol) showed that Nsp9 possesses highest binding affinity compared to other COVID-19 targets [40]. The SARS-CoV-2 symptoms (lowering in blood pressure followed by coma, increase in blood coagulation) associated with Nsp9 [46]. Targeted therapy of Nsp9 may be a potential therapy for COVID-19 infection. IVM showed binding interaction with LEU492, GLN493, GLY496, and TRYS05 amino acid residues of spike protein which support binding of hACE2 in the active site [44]. Therefore, IVM can be a drug candidate for SARS-CoV-2 to enter the human biological milieu via hACE2 [44] (see Table 2).

Proteases also showed significant interaction and stability with IVM during MD simulation experiment [41,44,47]. In very Recent, Sungur and group performed FDA approved drug repurposing against active site/allosteric binding sites of COVID-19 main protease. The obtained results indicated that IVM showed high binding affinity against main protease of COVID-19 [48]. Gonzalez-Paz et al. carried out a blind-docking experiment to predict the binding interactions of the B1a and B1b forms of IVM (Fig. 1) to main protease (3CLpro), indicating that IVM B1a binds with a good affinity than IVM B1b [44]. Recently Mody et al. carried out computational molecular modeling study on 3987 FDA approved drugs, and 47 drugs were filtered to study their inhibitory effects on covid-19 specific 3-chymotrypsin like protease 3CLpro enzyme in vitro. Among filtered drug, IVM showed good inhibitory effect (IC50: 21.53 μM) against 3CLpro. The 100 ns MD simulation explained that the IVM may involve active form homodimeric of 3CLpro for its inhibitory activity [49]. Molecular docking/dynamic simulation results indicated that IVM is a multi-targeted drug. Binding interactions result suggested, Nsp9, spike protein and 3CLpro/Mpro are the most probable targets for defining mode of action of IVM (Figs. 4 and 5). MD simulation-based analysis (RMSD, RMFS, radius of gyration, different energy profile, etc.), will provide atomistic level insights and benefit in designing of IVM based derivatives against COVID-19 targets.

4. Future directions

The FDA approved antiparasitic drug IVM has been used in the treatment of some neglected tropical diseases. It has been investigated to evaluate its properties towards malaria transmission and has shown well tolerance. For antiviral properties approval from FDA is not granted [50-52]. Many clinical trials have been initiated to establish anti-COVID use of IVM due its promising effects like reduced mortality rate, reduced level of inflammatory markers, and early recovery among infected individuals [53-59]. IVM belongs to Biopharmaceutical classification system (BCS) Class II having high permeability and low solubility. The limitations associated with IVM approval as anti-COVID therapeutics are smaller sample size in most of the trials, varying dose and dosage schedule, lack of double or single blinded study, coadministration of other drugs affects evaluation of safety and efficacy of IVM, lack of details about SARS-CoV-2 infection, and improper explanation of study outcomes. In addition to this, IVM is available as only oral dosage and need to be improved for pharmacokinetiks as well as for targeted delivery.

IVM and associated adverse/side effects have been documented [60-63]. Further studies on use of IVM in SARS-CoV-2 infection are necessary to overcome the adverse effects mainly neurological, safety in pediatric patients and at various stages of pregnancy.

In addition to the ongoing efforts towards establishment of IVM for its antiviral properties against SARS-CoV-2, medicinal chemistry groups are focusing on structural optimization of the lead nuclei. Literature has documented investigation of IVM hybrids (in vivo and in vitro antimalarial agents), synthesis of Avermectin B1a, improved hydrophilicity for dipeptide and carbohydrate IVM B1 derivatives, and sodium 5-sulfate-IVM and disodium 4”,5-disulphate-IVM [64-67]. Some of the possible strategies which can be adopted includes preparation of IVM hybrid analogs with aim to improve pharmacokinetic and pharmacodynamic profile against SARS-CoV-2. Furthermore, use of IVM as inhalation will help to provide high concentration of drug where viral load can be...
various agents are in use based on their clinical outcomes.

Clinical trials reporting use of IVM and its formulations for SARS-CoV-2 infection are described in Table 3.

Table 3

| ClinicalTrials.gov Identifier | Details | Ref. |
|-----------------------------|--------|-----|
| NCT04510233                | Ivermectin Nasal Spray for COVID-19 patients (12 mg, oral stat) | [69] |
| NCT04920942                | Ivermectin treatment efficacy in COVID-19 high risk patients (0.4 mg/kg/day for 5 days) | [70] |
| NCT04425850                | Topical Ivermectin and Carrageenan to prevent contagion of COVID-19 | [71] |
| NCT04523831                | Clinical trials of Ivermectin plus Doxycycline for the treatment of confirmed COVID-19 infection | [72] |
| NCT04381884                | Ivermectin effect on SARS-CoV-2 replication in patients with COVID-19 (600 μg/kg/once daily plus standard care) | [73] |
| NCT047234459               | Efficacy of nano-Ivermectin impregnated masks in prevention of COVID-19 among healthy contacts and medical staff | [74] |
| NCT04646109                | Ivermectin for severe COVID-19 management (200 μg/kg/day) | [75] |
| NCT04661053                | Inhaled Ivermectin and COVID-19 (6 mg BID for 3 days) | [76] |
| NCT04739410                | Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 patients (12 mg, oral stat) | [77] |

5. Clinical outcomes

Worldwide for effective management of SARS-CoV-2 infection various agents are in use based on their in vitro or observational studies. Among the reported more than 300 clinical trials evaluating efficacy of anti-COVID therapeutics, 81 report use of IVM and its formulations as therapeutic option for the treatment of SARS-CoV-2 infection are reported (Table 3). For these trials results or primary end points are published and few will be reported in the coming months. Few trials report no significant improvement in the time required to resolve the symptoms [68]. The associated limitation with reported trials such as significantly different results for primary and secondary end points, and instead of virological assessments clinical characteristics reflecting viral activity were measured. More trials may be required in the coming time to understand the mechanism of IVM for other clinically relevant outcomes.

6. Conclusion

The anti-helminthic drug IVM having diverse biological activity profile has been investigated for its therapeutic potential against SARS-CoV-2 infection. IVM has been classified as host-directed agent. It shows host immunomodulatory properties and has been found to inhibit the IMPα/β-mediated nuclear import of viral proteins. For the efficient management of COVID-19 and its possible future outbreaks it is required to understand the new variants of SARS-CoV-2 and the possibility for target-based drug design. Over the past 1½ year more than 1400 structures of SARS-CoV-2 proteins have been deposited in the Protein Data Bank (PDB) and have contributed significantly to provide biological/virtual insight to design anti-COVID drugs. Using protein structures data, various computational studies have been done to explore IVM binding mechanism and docking/dynamic simulation of IVM with different targets suggested NS5, spike protein and main proteases are the possible targets for defining mechanism of IVM. We hope this review will improve the understanding of the mechanism of IVM against SARS-CoV-2.

Author contribution

V.M.P. and S.V. designed the review, analyzed the data and articles, performed the analyses, and wrote the manuscript, with input from N.M. All authors reviewed the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] F.L. Njoo, C.E. Hack, J. Oosting, L. Luyendijk, J.S. Stilma, A. Klijnstra, C-reactive protein and interleukin-6 are elevated in onchocherciasis patients after ivermectin treatment, J. Infect. Dis. 170 (1994) 663–668.
[2] E. Mazzagola, M. Pezzullo, T.D. Burghgraave, et al., Ivermectinca's potient inhibitor of flavivirus replication specifically targetingNS3 helicase activity: new prospects for an old drug, J. Antimicrob. Chemother. 67 (2012) 1884–1894.
[3] F.S. Varghese, P. Kaukinen, S. Glasker, et al., Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses, Antivir. Res. 126 (2016) 117–124.
[4] R. Laing, V. Gillan, E. Devaney, Ivermectin - old drug, new tricks? Trends Parasitol. 33 (2017) 463–472.
[5] T.M. Tessier, M.J. Dodge, et al., Viral appropriation: laying claim to host nuclear transport machinery, Cells 8 (2019) 1–23.
[6] F. Heidary, R. Gharabaghi, Ivermectin: a systematic review from antiviral effects to worldwide for effective management of SARS-CoV-2 infection.
[7] E. Yamasmit, et al., Efficacy and Safety of ivermectin against Dengue Infection: a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial. He 34th Annual Meeting the Royal College of Physicians of Thailand, Internal Medicine and One Health, Chonburi, Thailand, 2018.
[8] L. Caly, J.D. Druce, M.G. Catton, D.A. Jans, K.M. Wagstaff, The FDA approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antivir. Res. (2020) 107487.
[9] R. Laing, V. Gillan, E. Devaney, Ivermectin- Old drug, new tricks? Trends Parasitol. 33 (2017) 463–472.
[10] A.J. Wolstenholme, A.T. Rogers, Glutamate-gated chloride channels and the mode of action of the avermectin/milbemycin anthelmintics, Parasitology 131 (Suppl) (2005) S85–S95.
[11] V. Golt, L. Magar, D. Dornfeld, et al., Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNA import, Sci. Rep. (2016) 23138.
[12] L. Lindingberg, C. Pinkham, A. Baer, et al., Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication, Antivir. Res. 100 (3) (2013) 662–672.
[13] M.Y.F. Tay, J.E. Fraser, W.K.K. Chan, et al., Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin, Antivir. Res. 99 (3) (2013) 301–306.
[14] K.M. Wagstaff, S.M. Rawlinson, A.C. Hears, et al., An AlphaScreen(R)-based assay for high-throughput screening for specific inhibitors of nuclear import, J. Biolum. Screen 16 (2) (2011) 192–200.
[15] K.M. Wagstaff, H. Sivakumar, S.M. Heaton, et al., Ivermectin is a specific inhibitor of importin alpha/beta mediated nuclear import able to inhibit replication of HIV-1 and dengue virus, Biochem. J. 443 (3) (2012) 851–856.
[16] E. Mazzagola, M. Pezzullo, T. De Burghgraeve, et al., Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug, J. Antimicrob. Chemother. 67 (2012) 1884–1894.
[17] N. Freitas, C. Cunha, Mechanisms and signals for the nuclear import of proteins, Curr. Genom. 10 (2009) 550–557.
[18] K. Lott, G. Cingolani, The importin α binding domain as a master regulator of nucleocytoplasmic transport, Biochim. Biophys. Acta 1813 (2011) 1578–1592.
[19] T.M. Tessier, M.J. Dodge, et al., Viral appropriation: laying claim to host nuclear transport machinery, Cells 8 (2019) 1–23.
[20] M. Oka, Y. Yoneda, Importin α functions as a nuclear transportfactor and beyond, Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 94 (2018) 274–274.
[21] M.Y. Tay, J.E. Fraser, W.K.K. Chan, et al., Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin, Antivir. Res. 99 (3) (2013) 301–306.
[22] S.N.Y. Yang, S.C. Atkinson, C. Wang, et al., The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β heterodimer, Antivir. Res. 2 (2020) 104766.
Ivermectin as a potential anti-SARS-CoV-2 agent. Curr. Opin. Investig. Drugs. 4 (2013) 93.

S. Omura, A. Crump, Ivermectin: panacea for resource-poor communities? Trends Parasitol. 30 (2014) 445–455.

M.L. Fritz, P.Y. Siegert, E.D. Walker, M.N. Bayouh, J.R. Vuluke, J.R. Miller, Toxicity of bloodmeals from ivermectin-treated cattle to Anopheles gambiae s.l. Annu. Trop. Med. Parasitol. 103 (2009) 539–547.

K.L. Kirik, J.Q. Del Rosso, A.M. Layton, J. Schauer, Over 25 years of clinical experience with ivermectin: an overview of safety for an increasing number of indications. J. Drugs Dermatol. 15 (2016) 255–252.

S. Ahmed, M.M. Karim, A.G. Ross, et al., A five-course of ivermectin for the treatment of COVID-19 may reduce the duration of illness, Int. J. Infect. Dis. 103 (2020) 214–216.

A.Z.K. Chachar, K.A. Khan, M. Asif, K. Tanveer, R. Basri, Effectiveness of Ivermectin in SARS-COV-2/COVID-19 patients, Intern. J. Sci. 19 (2020) 31–35.

A.T.M.M. Chowdhury, M. Shabbar, M.R. Karim, J. Islam, D. Guo, S. He, A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID19 Patients. Research Square, Preprint, 2020.

P. Soto-Becerra, C. Calzquichio, Y. Hurtado-Roca, R.V. Araujo-Castillo, Real-world Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized COVID-19 Patients: Results of a Target Trial Simulation Using Observational Data from a Nationwide Healthcare System in Peru, medRxiv, 2020. Preprint.

H.A. Hashim, M.F. Mauad, A.W. Ranseed, D.F. Fatak, K.K. Kabah, A.S. Abudalimir, Controlled Randomized Clinical Trial on Using Ivermectin with Doxycycline for Treating COVID-19 Patients in Baghdad, medRxiv, Iraq, 2020. Preprint.

M.S. Isaee, N. Gheibi, P. Namdar, et al., Ivermectin as an Adjunct Treatment for Hospitalized Adult COVID-19 Patients: a Randomized Multi-Center Clinical Trial. Research Square, Preprint, 2020.

M.S.I. Khan, M.S.I. Khan, C.R. Debnath, et al., Ivermectin treatment may improve the prognosis of patients with COVID-19, Arch. Bronconeumol. 56 (2020) 828–830.

R.E. Chandler, Serious neurological adverse events after ivermectin do they occur beyond the indication of onchocerciasis? Am. J. Trop. Med. Hyg. 98 (2018) 382–388.

M. Pasque, B. Munoz, G. Poetschek, J. Foose, B.M. Greene, H.R. Taylor, Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution, Lancet 336 (1990) 1486–1489.

J.P. Cippaux, N. Gordon-Wendel, J. Garland, J.C. Emsold, Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy, Trans. R. Soc. Trop. Med. Hyg. 87 (1993) 318.

J.O. Gyapong, M.A. Chinbuah, M. Gyapong, Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis, Trop. Med. Int. Health 8 (2003) 1093–1101.

L. Singh, D. Fontinha, D. Francisco, A.M. Mendes, M. Predoeco, K. Singh, Molecular design and synthesis of ivermectin hybrids targeting hepatic and erythrocytic stages of plasmodium parasites, J. Med. Chem. 63 (4) (2020) 1750–1762.

S. Yamashita, D. Hayashi, A. Nakano, Y. Hayashi, M. Hiramatsu, Total synthesis of ivermectin B1a revisited, J. Antibiot. (Tokyo) 66 (2013) 29–40.

D. Kozlovsky, L. Naaman, M. Shahar, T. Klenerman, T. Reiner, et al., Ivermectin in severe COVID-19 and its potential role in the treatment of COVID-19, J. Med Chem. 63 (13) (2020) 828–830.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.

M. Chaimovski, B. Miller, J. Ben, E. Ginzburg, D. Herbert, S. Gona, et al., Ivermectin as an Adjunct Therapy for Hospitalized COVID-19 Patients, Efficacy of Anti-Respiratory Viral Therapy (Covid-19) in Hospitalized Patients. Research Square, Preprint, 2020.