Understanding the mechanisms of action of Ivermectin against SARS-CoV-2

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INTRODUCTION

Ivermectin was discovered in the late 1970's originating solely from a single microorganism that was isolated at the Kitasato Institute, Tokyo. It was introduced as a veterinary drug against internal and external parasites in livestock (Crump A and Omura S. 2011). In 1987 Ivermectin was approved by the FDA for human use as it was found to be highly effective to Onchocerciasis, Strongyloidiasis. Subsequently, it has been repurposed to successfully overcome several other human diseases like Ascariasis, cutaneous larva migrans, filariases, Gnathostomiasis and Trichuriasis, as well as the treatment of ectoparasitic infections, such as Pediculosis (lice infestation) and scabies (mite infestation) and new uses for it are continually being found (Ottesen EA and Campbell WC. 1994). Drug repurposing, drug redirecting, or drug reprofiling is defined as the identification of novel usages for existing drugs as in the case if Ivermectin.

In the last 8 years Ivermectin has been studied for its potential as an antiviral that has the potential of preventing integration of the nuclear material into the host cell. Further *in vitro* studied have shown vigorous antiviral action towards a whole range of 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) (Jans DA and Wagstaff KM. 2021), Semliki Forest virus (SFV), and Sindbis virus (SINV), Avian influenza A virus, Porcine Reproductive and Respiratory Syndrome virus (PRRSV), Human immunodeficiency virus type 1 (HIV-1) as well as DNA viruses such as Equine herpesvirus type 1 (EHV-1) and Pseudorabies virus (PRV). Moreover, it has shown to exhibit antibacterial and anticancer activities (Shuran K et al, 2020).

Ivermectin has shown to be safe at high dosages and frequent regimens. A study by Guzzo et al. showed that higher doses of ivermectin 120 mg (up to 2 μg/kg), taken once or at 180 mg (up to 3 μg/kg), taken in split doses over 1 week is well-tolerated and safe (Guzzo CA, et al. 2002),

Because if its safety it is likely that well over 200 million people will be taking the drug annually or semi-annually, via innovative globally coordinated Mass Drug Administration (MDA) programmes, throughout the next decade (Crump A and Omura S. 2011).

MECHANISMS OF ACTION

In general, the 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 (Zaidi AK and Dehgani-Mobaraki P. 2021)

In 2011 Wagstaff et al. suggested the potential of Ivermectin as an inhibitor of nuclear transport of viral proteins. This was confirmed a year later that Ivermectin also inhibits nuclear transport of viral proteins of HIV and Dengue virus in HeLa cells. This blocking action of the importation of viral nuclear proteins showed that Ivermectin prevented replication of HIV and subsequent viral 'death' (Wagstaff KM et al. 2012).

Numerous other studies have shown the role of Ivermectin on SARS-CoV-2 as seen in table 1.

ROLE OF IVERMECTIN AGAINST SARS-COV-2
A. DIRECT ACTION IN SARS-COV-2 Level 1: Action on SARS-Cov-2 entry References: (Lebner et al. 2020), (Eweas et al. 2021), (Choudhury et al. 2021) Level 2: Action on Importin (IMP) superfamily References: (Yang et al. 2020) Level 3: Action as an Ionophore References: (Rizzo et al. 2020)
B. ACTION ON HOST TARGETS FOR VIRAL REPLICATION Level 4: Action as an antiviral References: (Heidary et al. 2020) Level 5: Action on viral replication and assembly References: (Caly et al 2020), (Arshad et al. 2020), (Swagiary et al. 2020), (Ma et al. 2015), (Eweas et al. 2021) Level 6: Action on post-translational processing of viral polyproteins References: (Eweas et al. 2021) Level 7: Action on Karyopherin (KPNA/KPNB) receptors References: (Caly et al 2020),
C. ACTION ON HOST TARGETS FOR INFLAMMATION Level 8: Action on Interferon (INF) levels Reference: (Seth et al. 2016) Level 9: Action on Toll- like-Receptors (TLRs) References: (Zhang et al 2008) Level 10: Action on Nuclear Factor-κB (NF-κB) pathway References: (Jiang et al. 2019) (Zhang et al 2008) Level 11: Action on the JAK-STAT pathway, PAI-1 and COVID-19 sequalae References: (Matsuyama 2020) Level 12: Action on P21 activated Kinase 1 (PAL-1) Reference: (Dou et al. 2016) Level 13: Action on Interleukin-6 (IL-6) levels References: (Zhang et al 2008), (G D de Melo et al. 2020) Level 14: Action on allosteric modulation of P2X4 receptor References: (Layhadi et al. 2018) Level 15: Action on high mobility group box 1 (HMGB1) References: (Juarez et al. 2018) Level 16: Action as an immunomodulator on Lung tissue and olfaction References: (G D de Melo et al. 2020) Level 17: Action as an anti-inflammatory References: (Zhang et al 2008), (Ci et al. 2009), (Yan et al 2011)
D. ACTION ON OTHER HOST TARGETS Level 18: Action on Plasmin and Annexin A2 Reference: (Kamber Zaidi et al. 2020) (Matsuyama 2020) Level 19: Action on CD147 on the RBC Reference: (Scheim 2020) Level 20: Action on mitochondrial ATP under hypoxia on cardiac function Reference: (Nagai et al. 2017)

CONCLUSION

The role of Ivermectin in mitigating infection and disease progression has undoubtly been shown in both *in vivo* and *in vitro* studies and is a clear game changer in addressing this pandemic going forward.

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