“Ivermectin” - A Key in the Bunch of Keys to Unlock the Other Activities Including Educational Institutions in COVID-19 Pandemic

Dr. R. P. Pareek¹, Dr. Rajnish Saxena², Dr. Vaibhav Saxena³

¹MD, MPhil, FICP, Ex-Professor, Department of Pharmacy and Medical Consultant, Birla Institute of Technology and Science, Pilani (BITS Pilani), India
²MBBS, PGCDM, Dip. Diabetology, Consultant Diabetologist & Physician, Saxena Diabetes Care Centre, Ajmer, India
³MBBS, DNB (Gen. Medicine, Junior Resident), SDMH, Jaipur, India

*Author for correspondence: pareekrp[at]gmail.com

Abstract: The Coronavirus has caused a Pandemic leading to a total Lockdown the world over. With passage of time the process of unlocking has started all over and is being implemented in a stepwise manner. The Industry and Service sectors have opened with the risks involved but the Educational Institutions are yet to open in the major part of the world including low and middle income countries like India. An effective vaccine is the most important solution; still some more preventive measures have to be adopted for total protection of the students. Ivermectin is being used at some places for treatment of COVID-19, mainly on experimental basis. The results are encouraging and a serious thought should be given for using Ivermectin as a prophylaxis for SARS-CoV-2. Along with other preventive measures. It may be proving to be a key in the bunch of keys to unlock the world and Educational Institutions. The other keys in the bunch being masking, physical distancing, hand washing, steaming and vaccine.

Keywords: Coronavirus, COVID-19, Pandemic, Keys to Unlock, Vaccine, Social Distancing, Masking, Hand washing, Prophylaxis, Ivermectin

1. Introduction

One hundred years after the Spanish flu pandemic in 1918-20, the whole world is again facing devastation due to the Covid-19 (SARS CoV-2) pandemic. This virulent virus SARS CoV-2 has high infectivity, morbidity and remarkable fatality rate. No specific treatment or vaccine has been invented to save mankind yet. The whole world is on the brink of collapse due to the outbreak of COVID-19 with no solution to treat these cases with any specific drug. Extensive search for the Vaccine or effective treatment is going on while alarming infection and death toll is rising every day¹.

Scientists, physicians and concerned multidisciplinary professional including political leaders are united to explore a quick effective treatment and vaccine before it is too late. Empirical applications of some drugs have been assumed to work with success, but without having a clinical trial, they cannot be validated. Until anything comes up, it might be useful to repurpose old therapies which could be effective against the virus².

SARS-CoV-2, a small 100 nm virus has taken the world by surprise and is still an unknown enemy.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus that causes a severe acute respiratory syndrome. Initially, it was called the novel Coronavirus and later named severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) due to its similar characteristics with severe acute respiratory syndrome Coronavirus 1 (SARS-CoV-1)³⁻⁵. The virus was named officially, by World Health Organization, as COVID-19 and a global health emergency. The first known case of infection was recorded in early December 2019 and subsequently spread to various continents, including Europe and the United States⁶,⁷.

This novel coronavirus 2019-nCoV was first identified in the state of Wuhan, China, at the end of 2019. Corona viruses are basically a group of viruses containing non segmented, single-stranded RNA. These groups of viruses caused several outbreaks around the world, like ‘Severe Acute Respiratory Syndrome (SARS) pandemicin 2002-2003 and the ‘Middle East Respiratory Syndrome (MERS) outbreak in South Korea in 2015. But most recently, COVID-19 triggered an outbreak in China in December 2019, subsequently become pandemic. Though some of corona patient reached in to devastating epidemics outcome, but others manifested mild to moderate respiratory infections, like the common cold⁸.

India is now placed at 2nd position in terms of the reported cases and reached the top place in the number of new cases per day. An affordable and safe treatment is still not available and various trials are in process. Some already existing drugs have been repurposed for the treatment and results from large studies are awaited.

2. Review of Literature for Ivermectin

Many drugs are in clinical trials across the world, including favipiravir and ivermectin, among others⁹.
Due to unavailability of effective therapeutic agents and the anticipated time lag between the speed of spread of the SARS-CoV-2 and the discovery of effective vaccines against corona virus disease COVID-19, various available anti-viral, anti-bacterial and anti-malarial drugs have been repurposedly used by physicians all over the world, with the hope to cut-down the huge human death-tolls and sufferings. Available evidences did not convincingly advocate their clinical use, though some favourable reports exist amid the clinical context of COVID-19, but few of these evidences are retracted.

Ivermectin is a versatile drug with unique characteristics, which make it interesting also for basic and applied research (in particular for drug repurposing): it seems to reveal an antibacterial\textsuperscript{13,12} antiviral, and anticancer activity\textsuperscript{13,14} besides being potentially useful for the treatment of some chronic pathologies\textsuperscript{15,16,17} result of an action on a wide range of cellular targets.

Ivermectin is a well-known anthelmintic agent from the late-1970s. In recent times, the antiviral function of ivermectin has been discovered. Already its effectiveness against certain flavivirus (dengue fever, Japanese encephalitis and tick-borne encephalitis virus) and chikungunya virus has been demonstrated in vitro. Since then the same activity has been assessed in numerous other viral infections. Off lately its potency has been recognized in eliminating coronavirus in vitro\textsuperscript{18}.

Because of the recent in vitro observation of ivermectin’s inhibitory effect against replication of SARS-CoV-2 in first 48 hours and the in vitro and possible clinical utility of hydroxychloroquine and ivermectin, there arise the scope for clinical trials and then re-purposive use of ivermectin in COVID-19\textsuperscript{19-22}.

Some specialists have revisited some of the old molecules & have found Ivermectin, originally introduced as an anthelmintic to be an effective, safe and affordable therapeutic option in Indian settings for prevention and treatment of COVID-19\textsuperscript{23,122}.

Ivermectin was discovered in 1975 and came into medical use in 1981. It is on the World Health Organization’s List of Essential Medicines\textsuperscript{24}. Ivermectin is a FDA approved drug, it is used for prevention, treatment, and control of river blindness (onchocerciasis) in populations where the disease is common. It is also used for treatment of Strongyloidosis, enterobiasis, Trichuristrichura, Loa Loa, Scabies, human lice, malaria and is also known to have wide-spectrum antiviral activity against number of viruses under in-vitro conditions\textsuperscript{25-28,31}. SARS-CoV-2 is a single stranded RNA virus which is closely related to SARS corona virus (SARS-CoV).

The actual behaviour of the virus and its pathogenicity are not yet fully understood. In a recent in vitro study, the Vero/hSLAM cells infected with the SARS-CoV-2 or COVID-19 virus were exposed to 5 μM ivermectin in 48 h, and a 5000-fold reduction in viral RNA compared with control was found\textsuperscript{19,40}. The results showed that treatment with Ivermectin effectively kills almost all viral particles within 48 h. The study was the first to assess the antiviral effect of ivermectin on COVID-19\textsuperscript{19}.

Ivermectin proposes many potentials effects to treat a range of diseases, with its antimicrobial, antiviral, and anti-cancer properties as a wonder drug. In vivo studies of animal models revealed a broad range of antiviral effects of ivermectin, however, clinical trials are necessary to appraise the potential efficacy of ivermectin in clinical setting\textsuperscript{32,33}.

The effectiveness against SARS-CoV-2 infection is due to its critical interaction of RNA viruses responsible for integrase protein nuclear import\textsuperscript{32,33}. A recent report suggests that Ivermectin reduces mortality rates in hospitalized patients with COVID-19\textsuperscript{34}.

Ivermectin was identified to inhibit the nuclear import of the HIV-1 integrase protein by interfering with its interaction with the nuclear α/β1 importin\textsuperscript{u1}. Additionally, ivermectin has been demonstrated to limit infection by other RNA viruses such as Dengue virus, West Nile Virus, and influenza through a similar mechanism affecting this same importin\textsuperscript{u2}. Studies have implicated a role for the α/β1 importin in SARS-CoV infection\textsuperscript{35}.

Sequestration in the pulmonary tissue Ivermectin was found to selectively concentrate in the pulmonary tissue, around 3 times the plasma concentration and is sequestrated in the pulmonary tissue with a long residence time\textsuperscript{36}.

Recent research has shown that Ivermectin possesses strong anti-viral properties\textsuperscript{120}. It has potential to convert RTPCR negative quickly\textsuperscript{19}. It can be used across the severity of COVID-19 especially in early viremic phase\textsuperscript{38}. It can be combined with other molecules of interest, like Hydroxychloroquine, azithromycin, doxycycline\textsuperscript{124}. Ivermectin is affordable, easily available, and safe without any major side effects\textsuperscript{38}.

No toxicity of Ivermectin was observed at any of the time points tested, in either the sample wells or in parallel tested drug alone samples. To further determine the effectiveness of ivermectin, cells infected with SARS-CoV-2 were treated with serial dilutions of ivermectin 2 h post infection and supernatant and cell pellets collected for real-time RT-PCR at 48 hours. Again, no toxicity was observed with Ivermectin at any of the concentrations tested\textsuperscript{39}. Taken together these results demonstrate that ivermectin has antiviral action against the SARS-CoV-2 clinical isolate in vitro, with a single dose able to control viral replication within 24–48 h in our system. It was hypothesised that this is likely through inhibiting IMPα/β1-mediated viral import of viral proteins, as shown for other RNA viruses\textsuperscript{31,43}.

A joint study conducted by Monash University Biomedicine Discovery Institute (MBD) and Peter Doherty Institute of Infection & Immunity in Australia was led by Dr. Kylie Wagstaff from MBD institute. He opined that single daily oral dose is safe and results in significant reduction in serum level of viral NS-1 protein without change in viremia or clinical benefit. He further mentioned “Even a single dose could essentially remove all viral RNA by 48 hours” (stops growth in cell culture effectively eradicating all genetic material of the virus)\textsuperscript{19}.
Very recent study by Caly et al had encouraging findings for the antiparasitic drug ivermectin which had shown considerable antiviral activity against CoV-2 in their in vitro experiments. Ivermectin may be the wonder drug for the current pandemic once the clinical trials are completed.59

With the limited clinical evidence available till date, Ivermectin has shown its promise in all phases of the disease and is being used both prophylactically and for treatment of all phases of disease from mild to severe.64

It appears Ivermectin and Doxycycline is safe and effective combination drug therapy in COVID-19 infected patients but need further extensive study to find out the scope of application on other groups of patients.45

The Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease. It has been reported that Ivermectin is a better choice for the treatment of patients with mild to moderate COVID-19 disease.45

A systematic review, showed antiviral effects of ivermectin on a broad range of RNA and DNA viruses and the study presented the possibility that ivermectin could be a useful antiviral agent in several viruses including those with positive-sense single-stranded RNA, in similar fashion.57

Since significant effectiveness of ivermectin is seen in the early stages of infection in experimental studies, it is proposed that ivermectin administration may be effective in the early stages or prevention.57

Ivermectin has previously been studied as a therapeutic option for viral infections with in vitro data showing some activity against a broad range of viruses, including HIV, Dengue, Influenza and Zikavirus.59,60 In a recent study, Wagstaff et al, demonstrated that Ivermectin was a potent in-vitro inhibitor of SARS-CoV-2, showing a 99.8% reduction in viral RNA after 48 hours.4 However, in-vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not previously been reported.59,60

Mechanism of action

Ivermectin, a well-known anti-helmintic agent from the late-1970s, causes stimulation of gamma amino butyric acid (GABA)-gated-CI–channels, leading to hyperpolarization, and resulting in paralysis of the infesting organism. Another mechanism that has been postulated for the same effect is the immunomodulation of host response. This is attained by the activation of neutrophils, increase in the levels of C-reactive protein and interleukin-6.52

In recent times, the antiviral function of ivermectin has been discovered, which appears to be intriguing. Already its effectiveness against certain flavivirus (dengue fever, Japanese encephalitis and tick-borne encephalitis virus) and chikungunya virus has been demonstrated in vitro.26,54 Since then the same activity has been assessed in numerous other viral infections. The exact mechanism to which this effect can be attributed to is yet to be validated, but the speculated method is inhibition of importin α/β mediated transport of viral proteins in and out of the nucleus.55 Importins, a type of karyopherins, exemplify a major class of soluble transport receptors which are involved in nucleo-cytoplasmic transit of various substrates.56

Caly et al.19 have recently shown that the drug also inhibits the replication of the SARS-CoV-2 virus in vitro, however not clarifying how it occurs. Since the causative agent of COVID-19 is an RNA virus, it can be reasonably expected an interference with the same proteins and the same molecular processes described above. However, ivermectin could prove to be a powerful antiviral, therefore also useful for a possible treatment of the new coronavirus associated syndrome, even from a new perspective. This could happen assuming its role as an ionophore agent, only hinted in the recent past but never fully described.13,17

Ivermectin is a specific inhibitor of importin-α/β-dependent nuclear transport and shows antiviral potential against several RNA viruses by blocking the nuclear localization of viral proteins. Since the replication of DNA viruses is in the nucleus, ivermectin may be functional against DNA virus infections if the DNA polymerase or other important viral proteins enter the nucleus via the importin-α/β-mediated pathway.61 Ivermectin was identified as a broad-spectrum inhibitor of importin-α/β-mediated nuclear import.19 By restraining nuclear transport of the integrase of HIV-1 and, the polymerase, non-structural protein 5, of dengue virus (DEV), ivermectin inhibits HIV-1 and DEV proliferation and thus exhibits antiviral potential in addition to its widely known anti-parasitic activity.19

Exact mechanism by which Ivermectin responded against the SARS CoV-2 virus is not known and was believed to be working similarly as it acted on other viruses. It was known to inhibit the nuclear import of viral and host proteins. As most of the RNA viruses are dependent upon IMPα/β1 during infection, Ivermectin acts on it and inhibits the import with the increase in antiviral response.18,63

Ivermectin binds to and destabilizes the IMPα/β1 heterodimer thereby preventing IMPα/β1 from binding to the viral proteinaind preventing it from entering the nucleus. This, likely, results in reduced inhibition of the antiviral responses, leading to a normal, more efficient antiviral response.63

The speculated inhibitory action of ivermectin on importin α/β mediated transport system, Basedon this conjecture, the role of ivermectin in eliminating Covid-19 can be assumed. Nevertheless, if compared with the other pharmacotherapeutic options for the management of Covid-19 infection, ivermectin may prove to have leverage over them. In addition to a different mechanism of action, there are other facets as well in which this drug may have an upper hand. For instance, the adverse effects associated with hydroxychloroquine (irreversible retinal damage, prolong QT interval, myopathy, neuropathy).18

Ivermectin is a broad spectrum anti-parasitic agent69 seems to have some anti-viral activities against a large number of viruses66-69 in vitro. Originally identified as an inhibitor of interaction between the human immunodeficiency virus-
1(HIV-1) integrase protein (IN) and the importin (IMP) δ/β1 heterodimer responsible for IN nuclear import. Studies on SARS-CoV proteins have revealed a potential role for IMPδ/β1 during infection in signal dependent nucleocytoplasmic shuttling of the SARS-CoV nucleocapsid protein, that may impact host cell division. Addition of the SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the STAT1 transcription factor by sequestering IMPδ/β1 on thorough ER/Golgi membrane. Taken together, these reports suggested that Ivermectin’s nuclear transport inhibitory activity may be active against SARS-CoV-2.

Studies revealed that ivermectin as a broad-spectrum drug with high lipid solubility possesses numerous effects on parasites, nematodes, arthropods, flavivirus, mycobacteria, and mammals through a variety of mechanisms. In addition to having antiparasitic and antiviral effects, this drug also causes immunomodulation in the host.

Ivermectin mechanism of action Sequestration of the SARS-CoV-2 viral nucleocapsid protein (NCP) into the host nucleus through the nuclear-pore-complex is a vital step in viral pathogenesis and defence against host immune response.

Regarding its role as an antiviral agent, its efficacy has been demonstrated on several viruses, both in vitro and in vivo. Among the many mechanisms by which it performs its function, the most consolidated one sees ivermectin as an inhibitor of nuclear transport mediated by the importin α/β1 heterodimer, responsible for the translocation of various viral species proteins (HIV-1, SV40), indispensable for their replication. This inhibition appears to affect a considerable number of RNA viruses, such as Dengue Virus 1-4 (DENV), West Nile Virus (WNV), Venezuelan Equine Encephalitis Virus (VEEV), and Influenza. In addition, ivermectin has been shown to be effective against the Pseudorabies virus (PRV, with a DNA-based genome), both in vitro and in vivo, using the same mechanism.

The proposed anti-SARS-CoV-2 action of ivermectin involves the binding of ivermectin to the Impo/β1 heterodimer, leading to its destabilization and prevention of Impo/β1binding to the viral proteins. This prevents viral proteins from entering the nucleus, thereby reducing the inhibition of antiviral responses and leading to an efficient antiviral response. The antiviral activity of ivermectin is also found to be related to other mechanisms. Ivermectin has been reported to suppress the replication of the pseudorabies virus by inhibiting the nuclear import of UL42 (an accessory subunit of DNA polymerase). A similar mechanism of inhibition was reported for another DNA virus, bovine herpesvirus.  Ivermectin inhibits the nuclear localization signal-mediated import of capsid protein (Cap) of porcine circovirus. It is, therefore, necessary to identify the exact mechanism underlying the in vitro antiviral activity of ivermectin against SARS-CoV-2 to obtain an insight into the possible mechanism of infection.
whether processing of host microRNAs by these TRIMs influences infection biology, and whether some of these TRIMs could even process virus-encoded microRNAs.

Many TRIM proteins are induced by type I and type II interferons, which are crucial for many aspects of resistance to pathogens, and several are known to be required for the restriction of infection by lentiviruses.\(^{107}\)

The versatility of the TRIM proteins is due to their diversity, splicing variants, differences in tissue expression and subcellular localization, but also to the increasingly well understood interactions of their N-terminal and C-terminal domains with other proteins. Their biological effects are also reflected in their ability to interact directly with viral components, either alone or in combination with other cellular proteins, and to modulate signalling pathways that are triggered by the engagement of pattern-recognition receptors (PRRs). This downstream regulation affects the expression of both type I and type II Interferons, and of cytokines that are involved in proinflammatory responses and in promoting different aspects of the adaptive immune response.\(^{107}\)

Virus infection leads to the activation of transcription factor IRF3 and subsequent production of type I interferons, which induce the transcription of various antiviral genes called interferon-stimulated genes (ISGs) to eliminate viral infection. IRF3 activation requires phosphorylation, dimerization and nuclear translocation. However, the mechanisms for the termination of IRF3 activation in nucleus are elusive. It was reported that the identification of TRIM26 to negatively regulate IFN-β production and antiviral response by targeting nuclear IRF3. TRIM26 bound to IRF3 and promoted its K48-linked polyubiquitination and degradation in nucleus. TRIM26 degraded WT IRF3 and the constitutive active mutant IRF3 5D, but not the phosphorylation deficient mutant IRF3 5A. Furthermore, IRF3 mutant in the Nuclear Localization Signal (NLS), which could not move into nucleus, was not degraded by TRIM26.\(^{108}\)

Importantly, virus infection promoted TRIM26 nuclear translocation, which was required for IRF3 degradation. As a consequence, TRIM26 attenuated IFN-β promoter activation and IFN-β production downstream of TLR3/4, RLR and DNA sensing pathways. TRIM26 transgenic mice showed much less IRF3 activation and IFN-β production, while increased virus replication. A study reported a novel mechanism for the termination of IRF3 activation in nucleus through TRIM26-mediated IRF3 ubiquitination and degradation.\(^{108}\)

To directly confirm nuclear translocation of IRF3 and TRIM26 is required for IRF3 degradation, nuclear import inhibitor Ivermectin was used. Ivermectin treatment prevented the nuclear translocation of IRF3 after SeV infection. While, IRF3 phosphorylation was not impaired by Ivermectin treatment. Notably, inhibition of IRF3 nuclear translocation by Ivermectin abolished TRIM26-induced IRF3 degradation in SeV-infected cells and uninfected cells. Taken together, these results suggested that TRIM26 mediates ubiquitination and degradation of active IRF3 in the nucleus.\(^{108}\)

**Adverse reactions**

Ivermectin is well tolerated by uninfected humans. It is primarily metabolized in the liver by CYP450-3A47 and has a plasma half-life of 16 hours and is almost exclusively excreted in faeces with minimal clearance by the kidneys. Therefore, it does not require dose adjustment for people with renal failure. There have been some reports of a mild anticoagulation effect. However, this is usually not significant enough to alter coagulation parameters such as the prothrombin ratio. Side effects of oral Ivermectin are rare and usually minor. These include transient tachycardia, flushing, nausea and light headedness. More severe neurological side effects are theoretically possible in rare susceptible individuals.\(^{2}\)

Ivermectin has been demonstrated to be generally well tolerated. For the most part side effects have been mild and transient in nature.\(^{109}\)

The safety of Ivermectin in pregnant women has not been studied and such use is not recommended. Studies in animals have shown an increase in birth defects. Safety and effectiveness in children below 5 years and under 15 kg and pregnant women have not been established. Ivermectin passes into breast milk and use during breast feeding is not recommended.\(^{110}\)

No significant drug interactions with Ivermectin are recognized.

**Safety Profile**

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.\(^{111}\)

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the neonates.\(^{111}\)

Paediatric use Safety and effectiveness in paediatric patients weighing less than 15 kg have not been established.\(^{111}\)

Clinical studies of ivermectin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.\(^{111}\)

**International views:**

The Australian team that conducted the breakthrough lab study recently received funds from the Helmsley Charitable Trust to advance Ivermectin targeting COVID-19.\(^{19}\)

In Peru Ivermectin is now approved for at least mild cases of COVID-19.\(^{112}\)
In Bolivia Ivermectin is approved in the north-eastern Beni region.112

In Brazil, the city of Itajai, (population 200,000) handed out 1 to 3 doses of Ivermectin as prophylaxis/treatment to citizens. Estimates are that about 100k people took up on this offer, over 1m tablets were distributed. Honestly, there is no sign of a large effect here.119

The first case of novel coronavirus disease (COVID-19) in the Dominican Republic coincided with a period of political crisis. Distrust in governmental institutions shaped the critical phase of early response. Having a weak public health infrastructure and a lack of public trust, the Ministry of Health (MoH) began the fight against COVID-19 with a losing streak. Within 45 days of the first reported case, the political crisis and turmoil caused by “fake news” are limiting the capacity and success of the MoH response to the pandemic.114

Reports in the Dominican Republic have emerged showing that doctors are prescribing treatments and prophylaxis with regimens such as hydroxychloroquine plus azithromycin, tocilizumab115.e2 10 or Ivermectin,119(all based on news reports rather than MoH direction.

In India, Patna dose recommendation,117 said that due to the urgency of COVID pandemic, one cannot wait for a human trial hence, it was decided to propose a dose schedule for prevention and treatment of COVID-19 and it was named Patna Recommendation.117 For prevention it recommended 1 tablet of 3/6/9/12/15 mg depending on body weight in subjects exposed / likely to be exposed to CoV-2-health workers, frontline warriors including police/security personnel etc. and for treatment it was recommended to use for 5 to 10 days.117

Meanwhile, Bangladesh National Guidelines on Clinical Management of Coronavirus Disease-2019 reviewed its medication listF.118 People are using many drugs without any definite proof of benefit. So, high-powered, randomized, double-blind, placebo-controlled trials recruiting larger numbers of COVID-19 patients with different severity groups, is expected to provide a reliable statement in this issue. Till then, it would remain as a wake-up call towards the treating physicians to remain very much cautious in repurpose use of drugs against COVID-19 and “do no harm” to the patients.121

In India, The Indian Council of Medical Research (ICMR), the country’s apex medical research body, is reviewing the benefits of drugs ivermectin and doxycycline as potential therapy for Covid-19. The combination of these two drugs has been hailed by doctors in Bangladesh for yielding “astounding results”.

According to government portal Clinical Trials Registry India (CTRI), ivermectin is part of at least five ongoing trials in the country.

Max Hospital has registered a trial to study the effectiveness of ivermectin with ‘standard of care treatment versus standard of care treatment for Covid-19 cases’.

Another trial, registered by the Department of Medicine of Lady Hardinge Medical College in Delhi, will study the effects of anti-malarial drug hydroxychloroquine, ciclesonide, a drug used to treat asthma, and ivermectin in the treatment of moderate Covid-19 illness.

“We are closely studying the drug ivermectin and its possible efficacy against Covid19. It needs to be studied more closely,” a senior scientist at ICMR, told The Print.119

We can also stop the community transmission by asymptomatic carriers by treating the asymptomatic COVID-19 positive patients.2

Ivermectin therefore warrants further investigation for possible benefits in humans.40

Of course, confirmation of this statement requires human studies and clinical trials.47

Researchers have suggested different drug combination therapies for COVID-19 and have shown that Ivermectin is a better choice for the treatment of patients with mild to moderate COVID-19 disease o1

Triple therapy specialist Professor Thomas Borody, famous for curing peptic ulcers using a triple antibiotic therapy saving millions of lives, released the COVID-19 treatment protocol to Australian GPs, who can legally prescribe it to their COVID-19 positive patients, and can also prescribe it as a preventative medication. Borody says this could be the fastest and safest way to end the pandemic in Australia within 6-8 weeks126.

He says, “GPs can legally prescribe the therapy today as an “off label” treatment according to Australian Guidelines – a standard practice in medicine. In fact, more than 60% of prescriptions in Australia are “off-label”. It’s not a new concept. It’s happening every day to manage diseases and save lives.” Professor Borody continued: “We have a therapy that can fight COVID-19. The medications have been around for 50 years, they are cheap, FDA and TGA approved and have an outstanding safety profile. Why are we just waiting around for a vaccine? To save lives we should be using whatever is safe and available right now. We could lead the world in this fight126.

The other keys
Several months ago, we were not even familiar with the expression ‘social distancing’. But then the coronavirus pandemic began to spread across the world infecting hundreds of thousands of people. With the rising cases in India, we too have been urged to stay home and practise social distancing.

Medical experts in India knew that unless the exponential spread of the disease is stopped, healthcare services in India would be overwhelmed. Social distancing or Physical distancing was decided to be followed.82

This move can be backed by research conducted in Australia found that social distancing should be applied as early as possible before the virus starts spreading fast.
While testing and contact tracing are the domains of experts, all the public needs to do is practise social distancing.

COVID-19 spreads mainly among people who are in close contact (within about 6 feet) for a prolonged period.\textsuperscript{53-59}

Furthermore, research by the Indian Council of Medical Research has found that social distancing can reduce the spread of coronavirus by as much as 62%!

Face masks are crucial for preventing and control of Covid-19. Public use of face masks has been common in China and other nations in Asia since the beginning of the new coronavirus disease outbreak.\textsuperscript{34}

Cloth masks should be washed daily or after every extended use.

“Wash it with a detergent containing bleach or a bleach-like ingredient, dry it, and it is good to go,” said Rohde.\textsuperscript{44,51}

Masks, however, need to be worn properly, with a tight fit, and for all the time you are out, otherwise they would not offer any protection.\textsuperscript{51}

A Study shows that hand washing is key against COVID-19. University of Birmingham researchers have discovered that countries where people do not have a habit of washing their hands automatically tend to have a much higher exposure to coronavirus. The study reveals that countries where people do not have a habit of washing their hands automatically tend to have a much higher exposure to COVID-19. In the absence of a cure or vaccine, the current outbreak obliges humanity to find ways of reducing the potential risk of infection. Frequent handwashing with soap for at least 20 seconds is widely advised as a preventive measure against COVID-19.\textsuperscript{59}

COVID-19 has spread around the world with virtually no region left untouched. The speed of the spread and the alarming death rates have seen many countries and jurisdictions introduce measures to prevent the spread of COVID-19, and handwashing features very strongly in all of these. Handwashing has received considerable attention during the COVID-19 pandemic. It is a simple, primary preventive measure that most people can do independently. Handwashing with soap and water for at least 20 s or the use of alcohol-based hand sanitisers when soap and water are not available is the first line of defence in stopping the spread of infection.\textsuperscript{39}

Dry heat & and microwave-generated steam is also beneficial for preventing Covid-19 infection. It clears virus from para nasal space & throat and reduce the viral load.\textsuperscript{62}

The Covid-19 virus symptoms drastically reduced after the administration of steam. No further transmission was observed in such patients. Reversal of symptoms in the patients with Covid-19 is positive sign for steam therapy.\textsuperscript{123}

Ivermectin for prophylactic use:
With so many studies showing the value of Ivermectin for the treatment of Covid-19, some of them has also shown it to be a potential prophylactic drug.

With the limited clinical evidence available till date, Ivermectin has shown its promise in all phases of the disease and is being used both prophylactically and for treatment of all phases of disease from mild to severe.\textsuperscript{38}

Since significant effectiveness of ivermectin is seen in the early stages of infection in experimental studies, it is proposed that ivermectin administration may be effective in the early stages or prevention.\textsuperscript{47}

In India, the Uttar Pradesh government (UP) has directed the use of drug Ivermectin for treatment of COVID-19 patients, to replace HCQ. This drug will be used as a replacement for hydroxychloroquine. The Uttar Pradesh government has also approved the use of ivermectin tablet for the treatment and prevention of COVID-19. The drug will also be given to frontline health workers in COVID-19 hospitals, apart from people infected with COVID-19 and their contacts. It has to be used as 200 micrograms per kilogram of body weight on day 1, day 7 and day 30 for prevention from Covid-19. On an average it will be 12mg per dose.

Other states in India are also considering to use Ivermectin for prophylaxis.

Professor Thomas Borody, recently released the COVID-19 treatment protocol to Australian GPs, who can legally prescribe it to their COVID-19 positive patients, and can also prescribe it as a preventative medication\textsuperscript{126}.

Though, no clinical guidelines have been issued for the use of Ivermectin in India, doctors have been using it both for treatment of patients and prevention from Covid-19 by using it in those at risk.

3. Conclusion

The review of literature from various parts of the world strongly points towards potential effect of Ivermectin in treatment of Covid-19.\textsuperscript{120}

Hence, we can conclude the following:
1) Ivermectin exerts broad-spectrum antiviral activity against several animal and human viruses, including both RNA and DNA viruses.
2) The antiviral potential of ivermectin against various viruses is mediated via the targeting of the following: importin α/β-mediated nuclear transport of HIV-1 integrase and NS5 polymerase; NS3 helicase; nuclear import of UL42; and nuclear localization signal mediated nuclear import of Cap.
3) As SARS-CoV-2 is an RNA virus, the antiviral activity of ivermectin may be mediated through the inhibition of importin α/β-mediated nuclear transport of viral proteins.
4) The new revelations provide novel insights into the detailed antiviral mechanisms of TRIM56 and raise the
posibility of targeting this TRIM for development of broad antivirals.\textsuperscript{5,6} 

5) Notably, inhibition of IRF3 nuclear translocation by Ivermectin abolished TRIM26-induced IRF3 degradation in SeV-infected cells and uninfected cells.\textsuperscript{10,11} 

6) The clinical efficacy and utility of ivermectin in SARS-CoV-2-infected patients are unpredictable at this stage, as we are dealing with a completely novel virus. 

7) Wide clinical studies should be carried out to see the role of Ivermectin for prophylaxis. The proposed use of 12mg dose (200micrograms per kg.) on days 1,3,7, and 30 or days 1,7 and 30 can be considered with consensus. 

8) Ivermectin is a safe drug used for various conditions and it can be a possible off label drug for treatment of Covid-19. 

9) Ivermectin can be used as a prophylactic drug along with other measures to act as a Key to Unlock the world in the ongoing Covid-19 pandemic. 

References


[5] "Clinical findings in a group of patients infected with. The 2019 novel Coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series, Xiao-Wei Xu et al., BMJ, 2020, p. m792. 


[27] Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Götz V et al., Sci Rep. 2016;6:23138. doi: 10.1038/srep23138. [PMC free article] [PubMed] [CrossRef] [Google Scholar]


[48] A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. Abu Taib Mohmed et al., Research article Pre Print, DOI: https://doi.org/10.21203/rs.3.rs-38896/v1


[52] C-reactive protein and interleukin-6 are elevated in onchocerciasis patients after ivermectin treatment. Njoo FL et al., Clin Infec Dis. 2007;45(3):353–359. - PMC - PubMed


[56] Importin : functions as a nuclear transport factor and beyond. Oka M, Yoneda Y. ProcJpnAcadSer B: Phys

Volume 9 Issue 10, October 2020

www.ijsr.net

Licensed Under Creative Commons Attribution CC BY

Paper ID: SR201014195000 DOI: 10.21275/SR201014195000 947


The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Yang SNY et al (2020) Antiviral Res 177:104760


Overlapping and Distinct Molecular Determinants Dictating the Antiviral Activities of TRIM56 against Flavivirus and Corona virus, Baoming Liu et al., December 2014 Volume 88 Number 23 Journal of Virology p. 13821–13835


RNA-binding activity of TRIM25 is mediated by its PRY/SPRY domain and is required for ubiquitination, Choudhury NR et al., 2017, BMC. Biol. 15:105 [PubMed: 29117863]


Trim71 cooperates with microRNAs to repress Cdk1a expression and promote embryonic stem cell proliferation. Chang HM et al., 2012 Nat. Commun. 3:923 [PubMed: 22735451]


TRIM26 Negatively Regulates Interferon-β Production and Antiviral Response through Poly ubiquitination and Degradation of Nuclear IRF3 Peng Wang et al., PLOS Pathogens DOI:10.1371/journal.ppat.1004726 March 12, 2015 1 – 22


India e Trial Site News [Internet]. Ivermectin usage accelerates while the need for data is real: how about an ivermectin registry? [Internet]. [cited 19 July 2020]. Available from: https://www.trialsiteneWs.com/ivermectin-usageaccelerates-while-the-need-for-data-is-real-how-about-anivermectin-registry/; 2020 May.


[125] Orders from the Government of Uttar Pradesh, India. https://drive.google.com/file/d/1bX4O8QevnAwevTi jmFuENr23g5KBFCgv/view?usp=sharing.