International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

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

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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 day[1].

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 virus[2].

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 States[6,7]

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 cold[8].

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 others[9].

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 repurposively 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[10] 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[11,12] antiviral, and anticancer activity[13,14] , besides being potentially useful for the treatment of some chronic pathologies[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[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[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[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[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[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[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[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[30].

The effectiveness against SARS-CoV-2 infection is due to its critical interaction of RNA viruses responsible for integrase protein nuclear import[32,33]. A recent report suggests that Ivermectin reduces mortality rates in hospitalized patients with COVID-19[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[35] 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[36] u2. Studies have implicated a role for the α/β1 importin in SARS-CoV infection[37].

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[38.]

Recent research has shown that Ivermectin possesses strong anti-viral properties[120.] It has potential to convert RTPCR negative quickly[19].It can be used across the severity of COVID-19 especially in early viremic phase[38]. It can be combined with other molecules of interest, like Hydroxychloroquine, azithromycin, doxycycline[124]. Ivermectin is affordable, easily available, and safe without any major side effects.[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[40]. 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 nuclear import of viral proteins, as shown for other RNA viruses.[41-43]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)[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[45].

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.[38]

It appears Ivermectin and Doxycycline is safe and effective combination drug therapy in COVID- 19infected patients but need further extensive study to find out the scope of application on other groups of patients.[46]

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.[48]

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.[47]

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.[47]

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.[49,50] 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[19,50]

Mechanism of action

Ivermectin, a well-known anti-helminthic agent from the late-1970s, causes stimulation of gamma amino butyric acid (GABA)-gated-Cl−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 proteinand 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-parasiticagent[65] seems to have some anti-viral activities against a large number of viruses[66-69] in vitro. Originally identified as an inhibitor of interaction between the human immunodeficiency virus-

1(HIV-1) integrase protein (IN) and the importin (IMP) á/â1 heterodimer responsible for IN nuclear import.[70] Studies on SARS-CoV proteins have revealed a potential role for IMPá/â1 during infection in signal dependent nucleocytoplasmic shutting of the SARS-CoVnucleo capsid protein,[71-73] that may impact host cell division,[74,75] addition of the SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the STAT1 transcription factor by sequestering IMPá/â1 on thorough ER/ Golgi membrane.[76] 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,[77,78] 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.[79]

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.[19,38]

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.[17,80,81] This inhibition appears to affect a considerable number of RNA viruses,[83,84] such as Dengue Virus 1-4 (DENV),[85] West Nile Virus (WNV),[86] Venezuelan Equine Encephalitis Virus (VEEV),[87] and Influenza.[88] 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,[89] using the same mechanism.

The proposed anti-SARS-CoV-2 action of ivermectin involves the binding of ivermectin to the Impα/β1 heterodimer, leading to its destabilization and prevention of Impα/ 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.[19] 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).[89] A similar mechanism of inhibition was reported for another DNA virus, bovine herpesvirus.[18] Ivermectin inhibits the nuclear localization signal-mediated import of capsid protein (Cap) of porcine circovirus.[93] It is, therefore, necessary to identify the exact mechanism underlying the in vitro antiviral activity of ivermectin against SARSCoV- 2 to obtain an insight into the possible mechanism of infection.

The tripartite motif-containing (TRIM) proteins have emerged as a new class of host antiviral restriction factors, with several demonstrating roles in regulating innate antiviral responses. Altogether, TRIM56 is a versatile antiviral host factor that confers resistance to YFV, DENV2, and HCoV-OC43 through overlapping and distinct molecular determinants. It was demonstrated that TRIM56 restricts two medically important flavivirus, yellow fever virus (YFV) and dengue virus serotype 2 (DENV2), and a human coronavirus, HCoV-OC43.The novel findings in one of the study, for the first time, showed that human TRIM56 functions as a versatile antiviral restriction factor of human-pathogenic positive-strand RNA viruses.[94] It was also seen TRIM56 restricts flavivirus and HCoV-OC43 by targeting distinct stages of the viral life cycle. It was reported that the spectrum and specificity of the antiviral activities of TRIM56 against distinct positive-strand RNA viruses, broadened the scope of the role TRIM plays in antiviral immunity. It was important to note that TRIM56 accommodates these previously unrecognized antiviral functions via overlapping and distinct molecular determinants that dictate shared and disparate antiviral actions. These new revelations provide novel insights into the detailed antiviral mechanisms of TRIM56 and raise the possibility of targeting this TRIM for development of broad antivirals.[94]

Studies in recent years have demonstrated that many TRIM proteins play central roles in the host defence against viral infection. While some TRIM proteins directly antagonize distinct steps in the viral life cycle, others regulate signal transduction pathways induced by innate immune sensors, thereby modulating antiviral cytokine responses. Furthermore, TRIM proteins have been implicated in virus-induced autophagy and autophagy-mediated viral clearance.[95]Several TRIM proteins interfere with retroviral infection by directly inhibiting various stages of the infectious cycle. TRIM5α, which is probably the most well-characterized antiviral restriction factor, interacts with the intact viral capsid lattice and forms a complementary lattice that induces premature virion disassembly, blocking viral infection.[96]

Other viruses are also directly targeted by TRIM proteins. TRIM52 targets the NS2A protein of Japanese encephalitis virus for proteasomal degradation.[97] TRIM56 was reported to restrict infection by the flavivirus bovine viral diarrhoea virus, yellow fever virus, and dengue virus, as well as human coronavirus OC43 and HIV-1.[98-100]

Over the past decade we have learned many amazing things about TRIM proteins and their roles during viral infection. While it has been well established that TRIM proteins can act as antiviral restriction factors and master immune regulators, completely new functions of TRIM proteins have recently been discovered, such as their ability to regulate autophagy. Interestingly, emerging evidence also suggests that several TRIM proteins influence RNA metabolism or microRNA processing, or even have RNA-binding capacities themselves. For example, TRIM25 has RNA-binding activity,[101,102] and TRIM32, TRIM65, and TRIM71 have been described as regulators of microRNA processing and RNA interference.[103-106] It warrants further investigation

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 andtype II interferons, which are crucial for many aspects of resistance to pathogens, and several areknown 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 productionof type I interferons, which induce the transcription of various antiviral genes called interferonstimulated 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 thatthe 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 nucleartranslocation of IRF3 after SeVinfection. 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.[113]

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, tocilizumab[115],e2 10 or Ivermectin,[116]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 re-purposive 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 weeks[126].

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 fight[126].

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.[82,90,91]

COVID-19 spreads mainly among people who are in close contact (within about 6 feet) for a prolonged period.[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.[44]

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.[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.[64]

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.[29]

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.[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.[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.[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.[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.[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[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.[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

possibility of targeting this TRIM for development of broad antivirals.[94]

5) Notably, inhibition of IRF3 nuclear translocation by Ivermectin abolished TRIM26-induced IRF3 degradation in SeV-infected cells and uninfected cells. [108]
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 ofCovid-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

[1] Comparison of Viral Clearance between Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin in COVID-19 Patients, MA Rahman et al., Journal of Bangladesh College of Physicians and Surgeons, Vol. 38, COVID-19 (Supplement Issue), July 2020
[2] A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline, MT Alam et al, Journal of Bangladesh College of Physicians and Surgeons, Vol. 38, COVID-19 (Supplement Issue), July 2020
[3] A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Chan JF et al, The Lancet, 2020;395(10223):514–23.
[4] "Clinical features of familial clustering in patients infected with 2019 novel coronavirus in Wuhan. China", Li J et al. Virus Research,2020; 286:198043.
[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.
[6] World Health Organization declares global emergency: a review of the 2019 novel corona virus (COVID-19).SohrabiCet al., Int J Surg, 2020; 76:71–6. https://doi.org/ 10.1016/j.ijsu.2020.02.034.
[7] Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. Lu H, Stratton CW, Tang Y-W. , J Med Virol. 2020; 92:401–2. https://doi.org/10.1002/jmv.25678.
[8] A review on corona virus (Covid- 19),Shri Krishna et al. wjpls, 2020, Vol. 6, Issue 4, 109-115
[9] Coronavirus Disease 2019 (COVID-19) – An Overview, Ariful Basher et al., Journal of Bangladesh College of Physicians and Surgeons Vol. 38, COVID-19 (Supplement Issue), July 2020
[10] Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19 ,Rajter JC, Sherman M, Fattah N, Vogel F, Sacks J, Rajter J. ICON (Ivermectin in Covid Nineteen) study:. medRxiv. The Preprint Sarver for Health Sciences. June 10, 2020.
[11] Anthelmintic Ivermectin killMycobacterium tuberculosis, including multidrug-resistant clinical strains, Lim LE et al., Feb) Antimicrob Agents Chemother. 57(2):1040–1046, 2013
[12] In vitro activity of ivermectin against Staphylococcus aureus clinical isolates. Ashraf S, Chaudhry U, Raza A, Ghosh D, Zhao X, Antimicrob Resist Infect Control. 7:27, 2018
[13] The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug, Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A, Am J Cancer Res. 8(2):317–331, 2018
[14] Anti-parasitic drug ivermectin exhibits potent anticancer activity against gemcitabine-resistant cholangiocarcinoma in vitro, Intuyod Ket al., Anticancer Res. 39(9):4837–4843, 2019
[15] Ivermectin exhibits potent antimitotic activity. Ashraf S, Prichard R,Vet Parasitol. 226:1–4, 2016.
[16] Ventre E et al, Topical ivermectin improves allergic skin inflammation. Allergy. 72(8): 1212–1221,2017.
[17] Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action, EmanueleRizzo, Naunyn-Schmiedeberg, Archives of Pharmacology https://doi.org/10.1007/s00210-020-01902-5
[18] Ivermectin: potential candidate for the treatment of COVID-19, Gupta D et al.,Braz J Infect Dis. 2020; S1413e8670(20):30081e30087.https://doi.org/10.1016/j.bjid. 2020.06.002, [published online ahead of print, 2020 Jun 28].
[19] Caly L et al., The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research 2020; 178:104787.
[20] Hydroxychloroquine and ivermectin: A synergistic combination for COVID-19 chemoprophylaxis and treatment? Patr A, Fabbrocini G, J Am AcadDermatol; e221.June 2020
[21] Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: trends, scope and relevance, Choudhary R, Sharma AK. New Microbe and New Infect; 35: 100684, 2020
[22] US National Library of Medicine. Hydroxychloroquine and Ivermectin for the Treatment of COVID-19 Infection. ClinicalTrials.gov Identifier: NCT04391127. First Posted May 18, 2020. Last Updated June 12, 2020. (Accessed June 27, 2020)
[23] White paper on Ivermectin as a potential therapy for COVID-19 AgamVora et al 25 July 2020, Letter to the Editor Tuberculosis Association of India. Published by Elsevier https://doi.org/10.1016/j.ijtb.2020.07.031
[24] World Health Organization (2019). World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. hdl:10665/ 325771. WHO/MVP/EMP/IAU/2019.06. License: CC BYNC- SA 3.0 IGO.
[25] Evaluation of cytotoxicity and antiviral activity of ivermectin against Newcastle disease virus, Azeem S et al., Pak J Pharm Sci. 2015;28(2):597–602. [PubMed] [Google Scholar]

[26] Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. Mastrangelo E et al., J. Antimicrob. Chemother. 2012;67(8):1884–1894. doi: 10.1093/jac/dks147. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[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]
[28] Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication, Lundberg L et al., Antivir Res. 2013;100(3):662–672. [PubMed] [Google Scholar]
[29] 29.https://www.birmingham.ac.uk/news/latest/2020/03/handwashing-culture-covid-19.aspx
[30] Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen FatemehHeidary, Reza Gharebaghi, - The Journal of Antibiotics (2020) 73:593–602 https://doi.org/10.1038/s41429-020-0336-z
[31] "Ivermectin – Old Drug, New Tricks?" Laing, Roz, et al. Trends in Parasitology, vol. 33, no. 6, 2017, pp. 463-472.
[32] The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, Caly, Leon, et al.Antiviral Research, vol. 178, 2020, p. 104787.
[33] Antiviral treatment of COVID-19, SimsekYavuz et al. " Turkish Journal of Medical Sciences, vol. 50, no. SI-1, 2020, pp. 611-619.
[34] Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19." Rajter, Juliana C., et al. "ICON (Ivermectin in Covid Nineteen) study: 2020.
[35] "An AlphaScreen®-Based Assay for High-Throughput Screening for Specific Inhibitors of Nuclear Import."Wagstaff, Kylie M., et al.Journal of Bio molecular Screening, vol. 16, no. 2, Feb. 2011, pp. 192–200. PubMed, doi:10.1177/1087057110390360.
[36] "Nuclear Trafficking of Proteins from RNA Viruses: Potential Target for Antivirals?" Caly, Leon, et al. Antiviral Research, vol. 95, no. 3, Sept. 2012, pp. 202–06. ScienceDirect, doi:10.1016/j.antiviral.2012.06.008.
[37] "Nucleo-cytoplasmic Transport of Nucleocapsid Proteins of Enveloped RNA Viruses."Wulan, Wahyu N., et al. Frontiers in Microbiology, vol. 6, Frontiers, 2015. Frontiers, doi:10.3389/fmicb.2015.00553.
[38] The battle against COVID-19 pandemic: what we need to know before we "test fire" Ivermectin. Banerjee K, Nandy M, Dalai CK, Ahmed SN.Drug Res (Stuttg). 2020. https://doi.org/10. 1055/a-1185-8913.
[39] MamdoohAlzyood et al, J ClinNurs. 2020 May 14 : 10.1111/jocn.15313. doi: 10.1111/jocn.15313
[40] The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in Vitro, L. Caly, et al. Antiviral Research 178 (2020) 104787
[41] Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Tay, M.Y., et al., 2013. Antivir. Res. 99 (3), 301–306.
[42] Ivermectin is a specific inhibitor of importin alpha/betamediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Wagstaff, K.M., et al., 2012. Biochem. J. 443 (3), 851–856.
[43] The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. Yang, S.N.Y., et al., 2020. Antivir. Res. 104760.
[44] World Health Organization. Coronavirus disease (COVID-19) technical guidance: Infection prevention and control. Geneva: World Health Organization; 2020.
[45] COVID-19: Recent updates on SARS-CoV-2 and Preventing its Community Transmission in India by 21 Days Lockdown,Panwar&Mohite | J Pure Appl. Microbiol. | 14(suppl 1):921-929 | May 2020 Article 6204 | https://doi.org/10.22207/JPAM.14.SPL1.29 Print ISSN: 0973-7510; E-ISSN: 2581-690X
[46] Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. Lund berg, L., et al., 2013. Antivir. Res. 100(3),662–672.
[47] Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen FatemehHeidary, Reza Gharebaghi, - The Journal of Antibiotics (2020) 73:593–602 https://doi.org/10.1038/s41429-020-0336-z
[48] A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. Abu Taiub Mohammed et al , Research article Pre Print, DOI: https://doi.org/10.21203/rs.3.rs-38896/v1
[49] Broad-spectrum agents for flavivirus infections: dengue, Zika and beyond. Boldescu V et al., Nat Rev Drug Discov. 2017; 16:565-586.
[50] Ivermectin Is a Specific Inhibitor of Importin α/β-Mediated Nuclear Import Able to Inhibit Replication of HIV-1 and Dengue Virus. Wagstaff KM et al., Biochem. J. 2012; 443:851-856.
[51] World Health Organization. Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care. Geneva: World Health Organization; 2014.
[52] C-reactive protein and interleukin-6 are elevated in onchocerciasis patients after ivermectin treatment. Njoo FL et al., J Infect Dis. 1994;170:663–8, http://dx.doi.org/10.1093/infdis/170.3.663.
[53] The spread of influenza and other respiratory viruses: complexities and conjectures. Clin Infect Dis. 2007;45(3):353–359. - PMC - PubMed
[54] Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Varghese FS et al., Antiviral Res.2016; 126:117–24, http://dx.doi.org/10.1016/j.antiviral.2015.12.012.
[55] Viral appropriation: laying claim tohost nuclear transport machinery. Tessier TM, Dodge MJ, et al. Cells. 2019; 8:1–23.
[56] Importin : functions as a nuclear transport factor and beyond. Oka M, Yoneda Y. ProcJpnAcadSer B: Phys

Bio Sci.2018; 94:259–74, http://dx.doi.org/10.2183/pjab.94.018.
[57] Airborne transmission of communicable infection--the elusive pathway. Roy CJ, Milton DK. N Engl. J Med. 2004; 350(17):1710–1712. - PubMed
[58] Transmission of influenza a in human beings.Brankston G eT al. Lancet Infect Dis. 2007; 7(4):257–265. - PubMed
[59] Coronavirus Infection Prevention by Wearing Masks. Vo TS et al., Eurasian J Med. 2020 Jun;52(2):197-201. doi: 10.5152/eurasianjmed.2020.20056. PMID: 32612431; PMCID: PMC7311128.
[60] Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo, C.Lv et al. Antiviral Research 159 (2018) 55–62
[61] Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Wagstaff, Kylie M, Sivakumaran et al., 2012. Biochem. J. 443, 851–856.
[62] Dry heat and microwave-generated steam protocols for the rapid contamination of respiratory personal protective equipment in response to COVID-19-related shortages. Pascoe MJ et al., J Hosp Infect. 2020 Sep;106(1):10-19. doi: 10..1016/j.jhin.2020.07.008. Epub 2020 Jul 9. PMID: 32652212; PMCID: PMC7343662.
[63] Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: trends, scope and relevance. R. Choudharyand A.K. Sharma. New Microbes New Infect. 2020 May; 35: 100684. Published online 2020 Apr 22 doi: 10.1016/j.nmni.2020.100684
[64] Household Materials Selection for Homemade Cloth Face Coverings and Their Filtration Efficiency Enhancement with Triboelectric Charging. Zhao M et al. Nano Lett. 2020 Jul 8;20(7):5544-5552. doi: 10.1021/acs.nanolett.0c02211. Epub 2020 Jun 9. PMID: 32484683; PMCID: PMC7294826.
[65] The pharmacokinetics and interactions of ivermectin humans–amini review. Gonzalez Canga, A., et al., 2008. AAPS J. 10(1),42–46
[66] Influenza A viruses escapes from MxA restriction at the expense of elucient nuclear vRNPimport.Gotz, V., etal., 2016.Sci. Rep. 6, 23138.
[67] Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. Lund berg, L., et al., 2013. Antivir. Res. 100(3),662–672.
[68] Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Tay, M. Y., et al., 2013. Antivir. Res. 99(3),301–306.
[69] Ivermectin is a specific inhibitor of importin alpha/beta- mediated nuclear importable toinhibit replication of HIV-1 and dengue virus. Wagstaff, K. M., et al., 2012. Biochem. J., 443(3),851–856.
[70] An Alpha Screen (R)-based assay for high-through put screening for specific inhibitors of nuclear import. Wagstaff, K. M., et al., 2011. J. Biomol. Screen 16(2),192–200.
[71] Intra cellular localization of the severe acute respiratory syndrome corona virus nucleocapsidprotein: absence of nucleolar accumulation during infection and after expression as a recombinant protein in verocells, Rowland, R .R. et al., 2005.J. Virology 79(17),11507–11512.
[72] Nuclear / nucleolar localization properties of C-terminal nucleocapsid protein of SARS corona virus. Timani, K.A., et al., 2005. Virus Res. 114(1–2),23–34.
[73] Nucleo-cytoplasmic transport of nucleocapsid proteins of enveloped RNA viruses. Front. Wulan, W. N., et al., 2015. Microbiol. 6,553.
[74] The corona virus infectious bronchitis virus nucleoprotein localizes to the nucleolus.Hiscox, J. A., et al., 2001. J. Virol.75(1),506–512.
[75] Localization to the nucleolus is a common feature of corona virus nucleoproteins, and the protein may disrupt host cell division. Wurm, T., et al., 2001. J. Virol.75(19), 9345–9356.
[76] Severe acute respiratory syndrome corona virus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum / Golgi membrane. Frieman, M., et al., 2007.J. Virology. 81(18),9812–9824.
[77] Ivermectin, 'wonder drug' from Japan: the human use perspective. Crump A, Ōmura S. ProcJpnAcadSer B Phys. Biol. Sci. 2011; 87:13–28. https://doi.org/10.2183/pjab.87.13.
[78] The pharmacokinetics and interactions of ivermectin in humans–a mini-review. Gonzalez Canga A et al., AAPS J. 2008;10:42–6. https://doi.org/10.1208/s12248-007-9000-9.
[79] Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen Fatemeh Heidary, Reza Gharebaghi, - The Journal of Antibiotics (2020) 73:593–602 https://doi.org/10.1038/s41429-020-0336-z
[80] An Alpha Screen(R)-based assay for high-throughput screening for specific inhibitors of nuclear import. Wagstaff KM, Rawlinson SM, Hearps AC, Jans DA (2011) , Journal of biomolecular screening 16(2):192–200
[81] Ivermectin is a specific inhibitor of importin alpha/beta mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. WagstaffKM, Sivakumaran H et al., (2012) The Biochemical journal 443(3):851–856
[82] Comprehensive Analyses of SARS-CoV-2 Transmission in a Public Health Virology Laboratory. Zuckerman NS et al. Viruses. 2020 Aug 5;12(8):854. doi: 10.3390/v12080854. PMID: 32764372; PMCID: PMC7472171
[83] Inhibitors of nuclear transport. JansDA,MartinAJ, WagstaffKM (2019) CurrOpin Cell Biol. 58:50–60
[84] Nuclear trafficking of proteins from RNA viruses: potential target for anti-virals? Caly L, Wagstaff KM, Jans DA (2012) Antiviral research 95:202–206
[85] Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor ivermectin. Tay MY et al (2013) Antiviral Res 99(3):301–306

[86] The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Yang SNY et al (2020) Antiviral Res 177:104760
[87] Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. Lundberg L et al., (2013) Antiviral Res 100(3):662–672
[88] Influenza A viruses escapes from MxA restriction at the expense of efficient nuclear vRNP import.Gotz V et al (2016) Sci Rep 6:23138
[89] Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo.Lv C et al. (2018) Antiviral Res 159:55–62
[90] Fundamental protective mechanisms of face masks against droplet infections. Koehler CJ, Hain R. J Aerosol Sci. 2020 Oct; 148:105617. doi: 10.1016/j.jaerosci.2020.105617. Epub 2020 Jun 28. PMID: 32834103; PMCID: PMC7321045.
[91] Airborne Precautions: Ather B et al., 2020 Jun 28.Treasure Island (FL): Stat Pearls Publishing; 2020 Jan–.PMID: 30285363, Internet
[92] Ivermectin inhibits bovine herpesvirus 1 DNA polymerase nuclear import and interferes with viral replication. Raza S et al Microorganisms. 2020; 8(3):E409. https ://doi.org/10.3390/micro organ isms8 03040 9.
[93] Ivermectin treatment inhibits the replication of Porcine circovirus 2 (PCV2) in vitro and mitigates the impact of viral infection in piglets. Wang X et al., Virus Res. 2019; 2(263):80–6. https ://doi. org/10.1016/j.virus res.2019.01.010.
[94] Overlapping and Distinct Molecular Determinants Dictating the Antiviral Activities of TRIM56 against Flavivirus and Corona virus, Baoming Liu et al.,a December 2014 Volume 88 Number 23 Journal of Virology p. 13821–13835
[95] TRIM Proteins and Their Roles in Antiviral Host Defenses, Michiel van Gentet al., Annu Rev Virol. 2018 September 29; 5(1): 385–405. doi:10.1146/annurev-virology-092917-043323.
[96] TRIM5 structure, HIV-1 capsid recognition, and innate immune signalling. Curr. Opin.Grfftter MG, Luban J. 2012 Virology 2:142–50 [PubMed: 22482711]
[97] TRIM52 inhibits Japanese encephalitis virus replication by degrading the viral NS2A. Fan W et al., 2016 Sci. Rep 6:33698 [PubMed: 27667714]
[98] TRIM56 is a virus- and interferon-inducible E3 ubiquitin ligase that restricts pestivirus infection. Wang J, Liu B et al., 2011 J. Virology 85:3733–45 [PubMed: 21289118]
[99] Overlapping and distinct molecular determinants dictating the antiviral activities of TRIM56 against flavivirus and corona virus. Liu B, Li NL, Wang J, Shi PY, Wang T, et al. 2014 J.Virology 88:13821–35 [PubMed: 25253338]
[100] Identification of interferon-stimulated genes with antiretroviral activity. Kane M, Zang TM, Rihn SJ, Zhang F, Kueck T, et al. 2016 Cell Host Microbe 20:392–405 [PubMed: 27631702]
[101] 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]
[102] The RNA-binding protein repertoire of embryonic stem cells. Kwon SC, Yi H, Eichelbaum K, Föhr S, Fischer B, et al. 2013 Nat.Struct. Mol. Biol. 20:1122 [PubMed: 23912277]
[103] The TRIM-NHL protein TRIM32 activates micro-RNAs and prevents self-renewal in mouse neural progenitors.Schwamborn JC, Berezikov E, Knoblich JA. 2009 Cell 136:913–25 [PubMed: 19269368]
[104] TRIM65 regulates microRNA activity by ubiquitination of TNRC6. Li S, Wang L et al., 2014 PNAS 111:6970–75 [PubMed: 24778252]
[105] The let-7 target gene mouse lin−41 is a stem cell specific E3 ubiquitin ligase for the miRNA pathway protein Ago2.Rybak A, Fuchs H, Hadian K, Smirnova L, Wulczyn EA, et al. 2009 Nat. Cell Biol. 11:1411–20 [PubMed: 19898466]
[106] Trim71 cooperates with microRNAs to repress Cdkn1a expression and promote embryonic stem cell proliferation. Chang HM et al., 2012 Nat. Commun. 3:923 [PubMed: 22735451]
[107] TRIM family proteins and their emerging roles in innate Immunity, Keiko Ozato et al. Nat Rev Immunology. 2008 November; 8(11): 849–860. doi:10.1038/nri2413.
[108] 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
[109] Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects.Guzzo CA, Furtek CI, Porras AG, et al. J ClinPharmacology. 2002;42(10): 1122e1133. https://doi.org/10.1177/009127002401382731.
[110] Chemotherapy of Helminth infections (Chapter 51). McCarthy J., Laukas A., HotezP.J., Goodman Gilman's The Pharmacological Basis of Therapeutics, 12 Ed. New York: McGraw-Hill Companies, Inc; 2011. pg- 1456 Goodman and Gilman's The Pharmacological Basis of Therapeutics 12th edition, pg-1456
[111] Drugs@FDA: FDA-Approved Drugs. STROMECTOL® (ivermectin) tablets [Internet]. [cited: 2020 July 19] Available from: https://www.accessdata.fda.gov/scripts/cder/daf/ index.cfm?event¼overview.process&ApplNo¼050742.
[112] 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.
[113] https://www.reddit.com/r/ivermectin/comments/i7cbvz/itajai_city_and_ivermectin/
[114] Perspective Piece , COVID-19 and Fake News in the Dominican Republic, Leandro Tapia, Am. J. Trop.

Med. Hyg., 102(6), 2020, pp. 1172–1174 doi:10.4269/ajtmh.20-0234
[115] TratamientoSaca a Cinco de CuidadosIntensivos. List´ınDiario. Pantaleo´ n D, 2020. Availableat:https://listindiario.com/ la republica/2020/03/28/610777/tratamiento-saca-a-cincode- cuidados-intensivos.
[116] MedicamentoAyuda a 150 con COVID-19 en Centro de Puerto Plata. El Caribe. Ponce M, 2020. Available at: https:// www.elcaribe.com.do/2020/04/20/medicamento-ayuda-a-150- con-covid-19-en-centro-de-puerto-plata/.
[117] Can ivermectin be used to treat SARS-COVID-2? S. S. JhaCovid-19 Special Issue, March, 2020;1(1):14-16, http://doi.org/10.18231/j.ijirm.2020.019
[118] Disease Control Division. Directorate General of Health Services. Ministry of Health & Family Welfare. Government of the People's Republic of Bangladesh. National Guidelines on Clinical Management of Coronavirus Disease 2019 (COVID-19). Version 7.0. Published, 28 May 2020.
[119] https://www.trialsitenews.com/icmr-indias-national-research-agency-investigating-ivermectin-doxycycline-as-potential-treatment-for-covid-19/
[120] Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19, Sharun et al. Ann ClinMicrobiolAntimicrob (2020) 19:23 https://doi.org/10.1186/s12941-020-00368-w, Annals of Clinical Microbiology and Antimicrobials
[121] Re-purposive Use of Drugs in COVID-19: A Wake-up Call , MA Rahima, M Mostafib , Journal of Bangladesh College of Physicians and Surgeons Vol. 38, COVID-19 (Supplement Issue), July 2020 (J Bangladesh CollPhysSurg 2020; 38: 3-4) DOI: https://doi.org/10.3329/jbcps.v38i0.47438
[122] Perspectives for repurposing drugs for the coronavirus disease 2019. Cherian SS, Agrawal M et al., Indian J Med Res. 2020; 151(2 & 3):160e171. https://doi.org/10.4103/ijmr.IJMR_585_20.
[123] Use of steam as adjuvant treatment in Covid -19 Patients: an observational study-DilipPanwar, Balkrishana Adsul, RusyBhalla, H.K.Mahajan et all-Indian Medical Gazette- July 2020
[124] A comparative observational study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients [Preprint] [cited 2020 July 19].Chowdhury AT et al., Available from: https:// www.researchgate.net/publication/342159343; 2020.
[125] Orders from the Government of Uttar Pradesh, India. https://drive.google.com/file/d/1bX4O8QevnAvewTijmFuENr23g5KBFcgv/view?usp=sharing .
[126] https://www.businessnewsasia.com/20200819523177 35-ivermectin-triple-therapy-protocol-covid-19-released-australian-gps-infected-elderly-frontline-workers/