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## Review

# Combined therapy with ivermectin and doxycycline can effectively alleviate the cytokine storm of COVID-19 infection amid vaccination drive: A narrative review



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## ABSTRACT

An unprecedented global health crisis has developed due to the emergence of the mysterious coronavirus-2 of the severe acute respiratory syndrome, which has resulted in millions of deaths around the globe, as no therapy could control the 'cytokine storm'. Consequently, many vaccines have been developed and several others are being developed for this infection. Although most of the approved vaccines have been highly effective, many developing, and economically poor countries are still deprived of vaccination against SARS-CoV-2 due to the unequal distribution of vaccines worldwide. Furthermore, the uncertainty about the effectiveness of the available vaccines against the emerging mutants and variants also remains a matter of concern. Due to the multistep pathogenesis and unique features, combination therapy using safe immunomodulatory and antiviral drugs should be considered as the most effective and acceptable therapeutic regimen for this infection. Based on a thorough assessment of the literature, it was determined that it would be interesting to study the therapeutic potential of ivermectin and doxycycline, given their roles in several biological pathways involved in SARS CoV-2 pathogenesis. Following that, a comprehensive literature search was undertaken using Scopus, Web of Science, and Pubmed, depending on the inclusion and exclusion criteria. The present study provides a mechanism and comprehensive report, highlighting the role of combined therapy with ivermectin and doxycycline in alleviating the 'cytokine storm' of COVID-19 infection.

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## Introduction

A mysterious deadly disease which has originated in the Wuhan city of China gripped the whole world in no time. This disease was later designated as COVID-19 and declared a pandemic. About 245 million people were affected by this pandemic till November 17, 2021. It has taken the lives of 4.97 million people across the globe. It has left scientists, government authorities, and the whole world community clueless and helpless. Since the emergence of this infection, many existing drugs are being used in therapeutics for the treatment of this deadly disease. ‘Cytokine storm’, the hallmark of this incurable illness, is the cause of disease severity and has resulted in millions of deaths due to this deadly disease, as no therapy could control the ‘cytokine storm’. Such was the devastation, damage, and intensity of this pandemic that it prompted researchers and government authorities across the globe to initiate the development process for the vaccines vigorously. Consequently, many vaccines have been developed, and others are in the development stage against this infection. Although most vaccines are highly effective, many of the developing and economically poor countries are still deprived of vaccination against SARS-CoV-2 due to the unequal distribution of vaccines worldwide. Furthermore, the uncertainty about the effectiveness of currently available vaccines against the emerging mutants and variants also remains a matter of concern [1].

The current global trend in vaccination drive indicates that 100% immunization is a distant reality. In view of the above facts, drug therapy should be considered as the mainstay for the treatment of this disease. Thus, the currently available drugs are being explored. Accordingly, many types of drugs, such as antiviral, anti-inflammatory, antimalarial, anti-cytokine, interferons, etc., have been tried against this deadly infection [2]. Hydroxychloroquine was used in the initial phase of the disease, but it was found that the drug was not efficacious [3]. Among the different types of drugs used in practice, antiviral drugs have been extensively studied for the management of this infection. Remdesivir, a broad-spectrum antiviral, was the first drug approved for emergency use in hospitalized patients with COVID. It is also one of the most widely used drugs for COVID-19. However, the cost factor, the limited effectiveness in cytokine storms, and the availability issues of remdesivir, particularly in the Indian market, have paved the way for the other repurposed drugs. The multi-character and multistep pathogenesis of the disease indicates that the use of only one category of drugs viz. antiviral, antimalarial, anti-inflammatory, or immunomodulatory, will not be worthwhile for the management of this deadly infection. Given the unique nature of the disease, combination therapy with an antiviral and immunomodulatory drug should be considered as the most effective and acceptable therapeutic regimen for the management of this disease. Ivermectin has been used as an antiparasitic drug for the last 30 years. Many *in vitro* studies have reported that the drug is effective against COVID-19 infection. Consequently, many

clinical studies are in process to establish the efficacy and tolerability of the drug. The drug is well tolerated and is found to be safe [4,5]. Doxycycline is an antibiotic and belongs to the tetracycline family. It has been used in therapeutics for more than five decades. Studies have confirmed the broad-spectrum antibacterial, antiviral, anti-inflammatory, and immunomodulatory potential of doxycycline. Many combinations have been tried and tested for the treatment of SARS-CoV-2 infection, but none is effective as yet. Thus, it was thought worthwhile to explore the potential of ivermectin and doxycycline as the effective and safe ‘combination therapy’ based on their unique multiple-step mechanism of action.

## Methodology

A systematic search of PubMed, Google Scholar, Web of Science, and Science Direct was conducted from January 2020 to October 2021 for research on COVID-19 management using a combination of keywords, including “ivermectin + doxycycline + COVID-19,” “ivermectin + doxycycline + SARS-CoV-2,” and human studies, randomized controlled trials (RCT), prospective or retrospective cohort designs, case-control designs, case series, *in vitro* studies, and case reports. Only studies that mentioned the combination of ivermectin and doxycycline to manage the cytokine storm of COVID-19 were included in this review article.

## Ivermectin: a promising drug

Ivermectin is being used in therapeutics for more than three decades. Initially, it was considered an anthelmintic drug. The drug has been used effectively to treat lymphatic filariasis, head lice, strongyloidiasis, and river blindness [6,7]. Many studies have shown its effectiveness against various RNA viruses [8]. The drug has already been approved in Peru and Bolivia for its use in mild cases of COVID-19 [4]. The first path-breaking *in vitro* study with ivermectin was conducted in Australia [9]. The usefulness of ivermectin against SARS-CoV-2 infected cells has been established in the above-mentioned work. The drug was found to inhibit viral replication with a dose of 5  $\mu$ M. The viral load was found to be significantly reduced in the above study. A single dose controlled viral replication in this remarkable finding. Previously it has been established that the drug prevents HIV-1 replication by preventing the entry of integrase protein inside the nucleus [10]. Many RNA viruses depend upon their interaction with IMP  $\alpha/\beta$ 1 for their replication. Ivermectin acts as a broad-spectrum antibiotic by inhibiting the IMP  $\alpha/\beta$ 1, thereby suppressing the viral replication in all such infections, viz. influenza, chikungunya, and HIV [8,11]. Studies have shown that SARS-CoV infection and viral replication are mediated through the transporter IMP  $\alpha/\beta$ 1. Ivermectin has been used very widely in a clinical setting, and no serious adverse effects have been reported so far.

## Efficacy of ivermectin in viral infections

Ivermectin has been widely used in therapeutics as an anti-parasitic drug. It has also produced promising results against RNA and DNA viruses [8,11]. According to recent reports, the drug (1–2  $\mu\text{M}$ ) also suppresses the Zika virus [12]. The drug also significantly inhibited the dengue virus and was found to be safe at the concentrations used [8,9]. Leon Caley and his team conducted the first study on the use of ivermectin in COVID-19 infection. This was an in vitro study that reported a highly significant reduction in viral load. The researchers in this study have found that no toxicity with ivermectin was observed. The remarkable findings of the above study paved the way for the conduction of clinical trials on ivermectin. Currently, many studies are in process to find out the effectiveness of the drug alone or with other drugs. The encouraging results of the in vitro study prompted the researchers to conduct clinical studies to establish the therapeutic utility of the drug in the in vivo studies. A matched case-controlled study (186 matched pairs) conducted in AIIMS, Bhuvaneshwar, has reported a 73% reduction in COVID-19 with two doses (300  $\mu\text{g}$  at 72 h apart), suggesting its significant prophylactic activity. However, the single dose of ivermectin could not produce any significant prophylactic activity [13]. A retrospective cohort study ( $n = 280$ ) conducted in the USA showed that ivermectin produced significantly lower mortality in patients hospitalized in four Florida Hospitals [14]. Another observational study was conducted in the USA involving 1970 COVID-19 positive critically ill hospitalized patients from 169 hospitals. The study reported a marked improvement in the survival rate [15,16]. A random control clinical trial on COVID patients was conducted in Bangladesh in two groups. Patients in group A were treated with ivermectin and doxycycline, while the Group B patients were treated with hydroxychloroquine and azithromycin. After comparing the above groups with two different combinations, it was found that the results were better in group A. Furthermore, the adverse events were 31.67% in group A as compared to 46.43% in group B [6]. Reports of various studies involving the use of ivermectin against viral infections are presented in Table 1.

## The probable mechanism of action of ivermectin

Transport of proteins across the nuclear membrane is essential for carrying out important physiological processes such as cell division, differentiation, and multiplication.  $\text{IMP}\alpha/\beta 1$  is a type of transporter that transports various proteins from the cytoplasm to the nucleus. This process is accomplished with the help of nuclear localization signal and nuclear pore complex. It has been reported that  $\text{MP}\alpha/\beta 1$  is involved in the infectivity of SARS-CoV [17]. Thus, it can be considered that  $\text{IMP}\alpha/\beta 1$  may be involved in the etiology of SARS-CoV-2 [10,12,18–20].

The viral nucleocapsid protein (NCP) utilizes  $\text{IMP}\alpha/\beta 1$  for initiating its action. Ivermectin acts by selectively inhibiting the  $\alpha/\beta 1$  transporter, thus preventing the entry of NCP into the nucleus [21–23]. It is also considered that the drug selectively inhibits  $\text{IMP}\alpha/\beta 1$  and does not affect other nuclear import pathways. Ivermectin

has been reported to act by binding to  $\text{IMP}\alpha/\beta 1$  through NLS binding pocket [11]. Furthermore, the formation of  $\text{IMP}\alpha/\beta 1$  is also suppressed by the drug. It has also been hypothesized that two ivermectin molecules can interact to make it an ionophore [20].

## Doxycycline: a multifaced medication

Doxycycline is a derivative of tetracycline, which is widely used in infections caused by *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia psittaci*, *Klebsiella* species, and *acinetobacter*. The drug has also been used to treat other infections such as rickettsia infections, plague, and cholera [24]. The pharmacokinetic pattern of the drug is very impressive. The drug attains maximum plasma level within 2 h after drug administration. Literature survey has revealed that the drug does not produce any serious adverse effect during the ordinary course of therapy. Unlike other antibiotics, doxycycline does not produce diarrhea. Doxycycline acts by blocking/modifying the signaling pathways involved in viral infection in multiple steps.

### Efficacy of doxycycline in viral infections

Doxycycline (4.5  $\mu\text{M}$ ) has been reported to produce a significant reduction in viral load in SARS-CoV-2 infected cell lines [25]. The inhibitory activity was comparable with that produced by other drugs such as hydroxychloroquine, lopinavir, and azithromycin. This important study has also reported that doxycycline produced the above effect by the two-step mechanism, i.e., by preventing the viral entry and also by inhibiting the viral replication. It has also been found that the drug utilizes the same mechanism in suppressing the chikungunya virus, as mentioned above [26]. The drug has also been shown to inhibit dengue virus replication as well as its entry into the cells by inhibiting the dengue virus serine protease and also by suppressing the E2 envelope, respectively [27]. The case report of four high-risk patients with an associated pulmonary disease has shown that doxycycline treatment (100–200 mg daily) for 5–14 days had revealed a remarkable improvement in all symptoms of COVID-19 [28]. This was the first report of its kind on SARS-CoV-2 infected symptomatic patients. Studies have also reported that doxycycline prophylaxis was effective in preventing acute lung injury in experimentally induced H3N2 virulence in mice [29].

An important study was conducted on high-risk patients infected with SARS-CoV-2 who had suddenly developed clinical symptoms. These patients had at least one of the high-risk complications such as cardiac, lung, obesity, and diabetes. Doxycycline (100 mg orally or iv) was administered for 7 days in conjunction with a regular standard of care. It was observed that 85% of the patients were found to be recovered [30]. A report of various studies involving the use of Doxycycline against RNA viruses is reported in Table 2.

### Anti-inflammatory and immunomodulatory effects of doxycycline

Many studies have established the immunomodulatory and anti-inflammatory potential of doxycycline. An in vivo study has shown

**Table 1**  
Report of various studies involving the use of doxycycline against viral infections.

Type of study	Type of infection	Results/Remarks
<i>In vitro</i>	Dengue virus	Significant inhibition of infection. The drug inhibited serine protease enzymes and viral entry [26].
<i>In vivo</i> (RCT)	Dengue virus	A significant reduction in mortality from dengue hemorrhagic fever was observed. 11.2% mortality was found in doxycycline treated group (13/116) as compared to 20.9% mortality in untreated group (24/115) [33].
<i>In vivo</i> (Clinical study)	SARS-CoV-2	Administration of the drug resulted in marked reduction in all symptoms of COVID-19 [28].
<i>In vitro</i> study	SARS-CoV-2	Doxycycline inhibited infection. The results are comparable to those of other drugs [25].
<i>In vitro</i> study	Vesicular stomatitis virus	The drug significantly inhibited the virus [57].
<i>In vitro</i>	Chikungunya virus	Doxycycline significantly inhibited the virus [27].
<i>In vivo</i> (Clinical study)	Dengue virus	Suppression of cytokines [33].

**Table 2**  
Report of various studies involving the use of ivermectin against RNA viruses.

Type of study	Type of infection	Results/Remarks
Clinical study	SARS-CoV-2	Significantly lower mortality[15].
<i>In vitro</i> study (Australia)	SARS-CoV-2	Inhibition of virus[9].
observational registry-based study (169 Hospitals, 1970 patients)	COVID-19 critically ill patients	A significantly higher survival rate was observed[16].
Dominican Republic based clinical study	The early stage confirmed patients with COVID-19.	99% of the patients were recovered with 100–200 mcg/kg (initial dose) and 400 mcg/kg (final dose) (India – Trial Site News, 2020)
Bangladesh based clinical study (n = 60)	Symptomatic, confirmed SARS-CoV-2 infected patients	Ivermectin + doxycycline produced a better recovery rate as compared to hydroxychloroquine + azithromycin. The former combination also shortened the duration of recovery[6].
A matched controlled study (AIIMS Bhubaneswar)	Health care workers (positive and negative)	73% reduction in COVID-19 infection was observed after two doses of ivermectin prophylaxis (300 ug/kg given at an interval of 72 h)[13].
<i>In vitro</i> studies	Dengue virus (DENV)	Ivermectin (25–50 µM) produced an Inhibitory effect[11].
<i>In vitro</i> studies	Hendra virus (HEV)	Ivermectin (25–50 µM) produced an inhibitory effect[8].
<i>In vitro</i> studies	Zika virus (ZIKV) infected vero cells	Ivermectin potently inhibited the virus[12].
<i>In vitro</i> studies	Yellow fever virus	Ivermectin produced an Inhibitory effect[8].
<i>In vitro</i> studies	Human immunodeficiency virus type 1	An inhibitory effect was produced[8].
<i>In vitro</i> studies	Avian influenza A virus	Ivermectin inhibited the nuclear transmission of viral ribonucleoprotein complexes[8].
<i>In vitro</i> studies	Chikungunya virus (CHIKV)	Ivermectin inhibited the CHIKV infection in BHK-21 cell line[8].

that the drug (7–15 mg/l) inhibits the human neutrophil collagenase activity by 50%. In an important study, Johan et al. have reported that the function of the drug inhibits the polymorphonuclear leukocytes *in vitro* by binding to divalent cation [31].

Microglial activation in response to pathogens results in the release of pro-inflammatory molecules. An extensive study was conducted to investigate the effects of doxycycline on LPS-induced murine microglial activation [32]. It was an *in vitro* study in which 10 µM doxycycline was administered to rat microglial and neuronal cells, which were later subjected to hypoxic injury. The results have revealed that doxycycline suppressed activated microglial cells. It has also been confirmed that p38MAP kinase and NF-κB mediated pathways are involved in the above-mentioned activity. Thus, the drug inhibited the LPS induced activity of cytokines, NO as well as ROS. This effect was supported by the down-regulation of pro-inflammatory cytokines. Due to these multiple/multiple actions, doxycycline can be immensely beneficial in preventing or inhibiting COVID – 19 infection.

In an important study, doxycycline was administered to dengue hemorrhagic fever patients (n = 231) and observed for seven days. It was found that the level of IL-1β, IL-6, and TNF-α was increased in control groups, whereas the patients treated with doxycycline were found to exhibit low levels of these cytokines, which were statistically significant (P < 0.01) by day 3. There was a further reduction in the level of pro-inflammatory cytokines from day 3 to day 7. Furthermore, doxycycline treatment produced 46% reduction in mortality rate [33,34].

The toxic shock condition induced by superantigens is considered a hyper-inflammatory state caused by stimulation of the immune system. Consequently, the proinflammatory cytokines are released in such a state [35]. It has been confirmed that doxycycline exhibited the immunomodulatory effect by dose-dependent suppression of staphylococcal exotoxin-induced secretion of inflammatory mediators by the human WBC. Staphylococcal exotoxins were also found to be suppressed in the study above. The above findings establish the immunomodulatory activity of the drug.

Severe sepsis is a hyper-inflammatory state developed due to the excessive immune response and is the cause of mortality in severe pulmonary infections [36]. It has been established that there is a marked increase in the level of inflammatory cytokines as well as the MPO (oxidative enzyme) in septic conditions. A reduction in the level of glutathione is observed in septic conditions. Anasuya et al. have further confirmed the immunomodulatory activity of doxycycline when used in combination with the lower dose (100 mg/kg) of

ceftriaxone. The above combination also inhibited the CLP-induced increase in MPO levels. CLP-induced reduction in GSH level was also normalized by this treatment. The results of the above study have demonstrated the immunomodulatory and antioxidant potential of doxycycline.

Tetracyclines are found to be effective in various inflammatory disorders such as gingivitis, osteoarthritis, periodontitis, and pulmonary disorders [16,37]. Doxycycline has been reported that doxycycline can inhibit the process of inflammation by inhibiting the events of inflammation, viz. leukocyte adhesion and leukocyte migration [38,39]. The drug also inhibits the phospholipase A<sub>2</sub>, NF-κB, and I<sub>κ</sub>Bα [40–42]. Sun J et al. have reported that doxycycline regulates the p38 and ERK1/2/MAPK pathways, further validating its anti-inflammatory effects. Dysregulation of TXA<sub>2</sub> synthesis in inflammatory conditions favors hypercoagulation in the pulmonary capillaries. PGG<sub>2</sub> and PGH<sub>2</sub>, the precursors of TXA<sub>2</sub>, are derived from arachidonic acid by COX-1 and COX-2 [42]. It has been reported to inhibit the enzyme phospholipase A<sub>2</sub>, resulting in the reduced availability of arachidonic acid for the synthesis of PGG<sub>2</sub> and PGH<sub>2</sub>. Thus, doxycycline indirectly decreases the synthesis of thromboxane A<sub>2</sub> and thereby improves the thrombotic events in ALI and ARDS [40].

#### Doxycycline and matrix metalloproteinases

The severe acute respiratory syndrome coronavirus-2 utilizes matrix metalloproteinase-9 (MMP-9) for gaining its entry into the body. Doxycycline prevents the entry of the virus by inhibiting MMP-9. The unique structure of doxycycline with a four-ring core and many side groups makes it an important compound with pleiotropic actions. The lower part of the molecule is rich in oxygen, which helps in the chelation of metal ions, which greatly increases the binding of tetracyclines with different proteins. Hence, doxycycline has a higher binding capacity with different proteins as compared to other compounds. Therefore, this drug has a better ability to inhibit the metalloproteinases as compared to other similar compounds due to its higher chelation capacity for zinc ions present in the MMP-9 [43]. It has been established that the release of MMP-9 during acute lung injury is responsible for further magnifying the process of inflammation and thereby causing the destruction of lung tissue. Therefore, targeting MMP-9 could be an effective measure to manage this infection [44].

Matrix metalloproteinases (MMPs) are an important class of endopeptidases with a zinc-binding moiety in their catalytic site.

Previously, MMPs were responsible for degrading the extracellular matrix by the cleavage of collagens, fibronectin, and elastin. Later it was noticed that these proteinases have a wide range of physiological functions at the matrix and nonmatrix levels. But recently, it has been established that these important proteases play an important role in tissue homeostases, such as the remodeling of cells and tissues. More recently, it has also been established that MMPs have a role in interacting with the cell surface receptors [45]. They are also involved in regulating cytokines and chemokines. They are also involved in inflammation and tissue repair by regulating adhesion, migration, and angiogenesis. They produce a pathological state when their activity is uncontrolled.

Pulmonary epithelial damage is the hallmark of ARDS in COVID-19 infection, initiating the cascade of inflammatory events, resulting in lung parenchymal damage due to cytokine storm. There is an overexpression of MMPs, which produce remodeling of lung tissue. Nonspecific inhibition of MMPs can prevent further lung damage in ARDS/ALI. Therefore, nonspecific inhibitors of MMPs can be effective in managing ARDS in COVID infection. Studies have reported that doxycycline is one of the most widely used nonspecific inhibitors of MMPs [46].

Studies have shown that there is an increase in the expression of MMPs during infections. Thus, it is suggested that these molecules may enhance the virulence and pathogenicity in bacterial and viral infections. It has also been noted that the levels of MMP-9 are raised in septic conditions [45]. Batimastat and marimastat are first-generation MMP inhibitors, but they lack specificity. As a result, new MMP inhibitors with specificity in their action were developed, and doxycycline is an important drug in this category [45]. This drug has many other advantages as well. It does not produce GIT adverse effects and its bioavailability is also high.

#### *Cytokine storm and doxycycline*

The 'cytokine storm' is considered the hallmark of the COVID-19 illness and is the cause of millions of deaths due to this deadly disease. WBCs become hyperactive and inflammatory cytokines are released in this cytokine storm cascade. The epithelial cells of the lungs, as well as the endothelial lining of the capillaries surrounding the alveoli, are severely damaged and inflamed due to the hyperinflammatory and hyperimmune state. Damaged epithelium and endothelial cells release reactive oxygen species (ROS), which further damage the epithelial lining of alveoli and endothelial cells of the blood capillaries. Thus, a vicious cycle sets in, and there is overproduction of immune cells, cytokines, thromboxane  $A_2$  and ROS. Consequently, there is complete disruption of the alveolar-capillary barrier resulting in exacerbation of capillary permeability and hyperactivation of WBCs. Lung function declines profoundly due to pneumonia, pulmonary fibrosis, and edema. Finally, death ensues due to respiratory failure [46,47].

Lisa E et al. conducted a dose-escalation study on mice by adopting an unbiased modeling approach to study the molecular mechanisms involved in SARS-CoV pathology by conducting the proteomics analysis. This extensive study has reported that there is increased expression of the hyaline membrane in the acute pulmonary damage after SARS-CoV infection. Fibrin level was also found to be increased. The above findings suggest that there is dysregulation of the urokinase pathway resulting in abnormalities in coagulation. It is suggested that the above cascade of events may also be observed in SARS-CoV-2 infection. High fibrin and low surfactant levels enhance collagen deposition by stimulating the adherence and growth of fibroblasts, culminating in lung fibrosis [48,49]. Since there is no cure for fibrosis, it is important to develop therapeutic interventions that can prevent or slow the fibrotic process. Recent studies have shown that doxycycline has the potential to inhibit the MMPs responsible for the degradation of the

extracellular matrix of the lungs, thus reducing the process of fibrosis [50]. The AMP-activated kinase (AMPK) pathway is important in the maintenance of normal function and integrity of the endothelium in the lungs. It has been reported that AMPK activity was found to be decreased in bacterial endotoxin-induced lung injury in mice. Another study has reported that endothelial barrier dysfunction was observed in AMPK deficient mice. This study has also reported that the endothelial barrier integrity was improved by the pharmacologically induced activation of AMPK in these AMPK activities deficient mice. It has been established that MMPs stimulate the activity of TNF- $\alpha$ , which in term cause deactivation of AMPK. Therefore, by decreasing the activity of MMPs, AMPK can be activated, resulting in the maintenance of endothelial barrier function and integrity in the lungs [50].

It has been very widely accepted that MMPs are actively involved in pulmonary damage and ARDS [46]. A study has reported that SARS-CoV-2 infected ICU patients were found to have developed a pathology of thrombotic disorders. Studies have also revealed that inflammatory mediators are controlled by the MMPs [51].

Zinc is considered to be important in controlling the SARS-CoV-2 infection due to its diverse actions. It prevents replication of the SARS-CoV-2 RNA genome and also inhibits the translation process [52]. It also increases the interferon- $\alpha$  production, improving the immunity against the virus [53]. Since doxycycline can transport divalent cations such as zinc into infected host cells, it will produce its therapeutic effects against COVID-19 by increasing zinc transportation, thus preventing the replication of the virus [54–56].

#### **Conclusion**

The hallmark of the COVID-19 infectivity and severity is the 'cytokine storm' resulting in excessive irreversible damage to the lungs due to the uncontrolled release of proinflammatory cytokines. The end result is death due to severe pneumonia and multiorgan failure. Many mono-drug therapies have been tried with hardly any encouraging results. Simultaneously many different combination therapies such as lopinavir-ritonavir, hydroxychloroquine-azithromycin have also been used for the treatment of this infection, but with little benefit. The complex nature of the COVID-19 pathogenesis advocates the selection of drugs that can produce their effects through a multistep mechanism. Due to the diverse mechanisms of action of doxycycline and ivermectin, as mentioned in this review, this combination may help immensely in reducing the fatality of infection by preventing the cytokine storm.

In this review, the established therapeutic efficacy of ivermectin against various viral infections, including COVID infection, has been discussed in this review. The promising results of the drug against various infections suggests that the drug could be beneficial for the treatment of this mysterious disease. The established antiviral and immunomodulatory activity of doxycycline has also been presented in this report. The above-mentioned results suggest that the combined use of ivermectin and doxycycline can be useful in controlling the severity of the infection, as both drugs act synergistically in producing antiviral effects.

Furthermore, doxycycline will provide the additional benefit of reducing the cytokine storm. The clinical features of COVID-19 advocate that the combined use of antiviral and immunomodulatory drugs is expected to provide the best results against this deadly infection. In view of the three-step mechanism of action of this combination therapy, well-designed controlled trials need to be conducted to explore this combination therapy further so as to establish its therapeutic efficacy in the treatment of this infection. Based on the above findings, it can be concluded that due to its role in blocking / modifying various pathways (MMP-9, p38MAP kinase, and NF- $\kappa$ B) involved in the pathogenesis of COVID-19, doxycycline (200 mg daily) can be a very useful drug in reducing the severity of

**Table 3**  
Summary of the clinical trials based on ivermectin and doxycycline in COVID-19 [58–61].

Short title	Intervention	Condition	NCT number	Sponsor	Phase of Study	Outcomes	Status
An Outpatient Clinical Trial Using Ivermectin and Doxycycline in COVID-19 Positive Patients at High Risk to Prevent COVID-19 Related Hospitalization	Drug: Ivermectin Tablets Drug: Doxycycline Tablets Drug: Placebo	Covid-19	NCT04729140	Max Health, Subsero Health	Phase 4	Decreased admission rate to the hospital secondary to respiratory illness related to COVID-19 (5 week)	Recruiting
Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection	Drug: Ivermectin and Doxycycline Drug: Standard of care	Covid-19	NCT04523831	Dhaka Medical College	Phase 3	Body temperature remains normal for at least 3 days (ear temperature is lower than 37.5 °C). Respiratory symptoms are significantly improved. Lung imaging shows obvious improvement in lesions. There is no co-morbidities or complications which require hospitalization. SpO <sub>2</sub> > 93% without assisted oxygen inhalation.	Completed
Efficacy and Safety of Ivermectin and Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection.	Efficacy and Safety of Ivermectin and Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection.	Covid-19	NCT04407130	International Centre for Diarrhoeal Disease Research, Bangladesh	Phase 2	Presence of virus will be negative on Day 7 detected by RT PCR. Body temperature will be < 37.5 C by day 7 detected by Infrared thermometer. Remission of cough: No signs of cough showing respiratory rate within 12–20/ min. on day 7	Completed
Effectiveness of Ivermectin and Doxycycline on COVID-19 Patients	Drug: Ivermectin and Doxycycline Drug: Standard of care	Covid-19	NCT04591600	Alkarkh Health Directorate-Baghdad	Phase 1 Phase 2	The effect of the experimental drugs to reduce the mortality rate (death rate) of treated patients, rate of patients under treatment who undergo progression of disease to a more advanced stage	Completed

the disease, if used in combination with ivermectin (200–400 µg/kg daily).

A report of the clinical trials conducted on the combination therapy with ivermectin and doxycycline is presented in Table 3. The respiratory symptoms were found to be reduced and the body temperature was also normalized. After analyzing the results of the different clinical trials it is concluded that the use of ivermectin in combination with doxycycline can prove to be an effective, safe and affordable therapeutic regimen for relieving the cytokine storm of COVID-19 infection. Evaluation of the pharmacokinetic and pharmacological profile of the above drugs has revealed that the suitable oral and parenteral formulations of ivermectin+doxycycline can be developed for the management of COVID-19 patients particularly in the developing countries. Thus this combination finds immense industrial applicability in view of its cost effectiveness, safety and efficacy.

## References

- [1] Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol* 2021;21(10):626–36.
- [2] Cherian SS, Agrawal M, Basu A, Abraham P, Gangakhedkar RR, Bhargava B. Perspectives for repurposing drugs for the coronavirus disease 2019. *Indian J Med Res* 2020;151(2–3):160–71.
- [3] Mahévas M, Tran V-T, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ (Clin Res Ed)* 2020;369:m1844.
- [4] Vora A, Arora VK, Behera D, Tripathy SK. White paper on Ivermectin as a potential therapy for COVID-19. *Indian J Tuberc* 2020;67(3):448–51.
- [5] Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* 2002;42(10):1122–33.
- [6] Chowdhury, A.T. M., Shahbaz, M., Karim, M.R., Islam, J., Dan, G., & He, S. (2020). A comparative study on Ivermectin- Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. Unpublished. <https://doi.org/10.13140/RG.2.2.22193.81767/3>.
- [7] Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R, Singh BR, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. *Ann Clin Microbiol Antimicrob* 2020;19(1):23.
- [8] Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot* 2020;73(9):593–602.
- [9] Cally L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res* 2020;178(104787):104787.
- [10] Banerjee K, Nandy M, Dalai CK, Ahmed SN. The Battle against COVID 19 Pandemic: What we Need to Know Before we “Test Fire” Ivermectin. *Drug Res* 2020;70(8):337–40.
- [11] Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin  $\alpha/\beta$ -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J* 2012;443(3):851–6.
- [12] Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin  $\alpha/\beta$  heterodimer. *Antivir Res* 2020;177(104760):104760.
- [13] Behera P, Patro BK, Singh AK, Chandanshive PD, Kumar R, Pradhan SK, Pentapati SSK, Batmanabane G, Padhy BM, Bal S, Singh SR, Mohanty RR. Role of ivermectin in the prevention of COVID-19 infection among healthcare workers in India: A matched case-control study. *bioRxiv* 2020. <https://doi.org/10.1101/2020.10.29.20222661>
- [14] Cennimo David J. What is the roles of the antiparasitic drug niclosamide in the treatment of coronavirus disease 2019 (COVID-19)? *Medscape Com* 2021 (<https://www.medscape.com/answers/2500114-197513/what-is-the-role-of-the-antiparasitic-drug-ivermectin-in-the-treatment-of-coronavirus-disease-2019-covid-19>).
- [15] Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter J-J. Use of ivermectin is associated with lower mortality in hospitalized patients with Coronavirus disease 2019: The ivermectin in COVID nineteen study. *Chest* 2021;159(1):85–92.
- [16] Patel A, Khande H, Periasamy H, Mokale S. Immunomodulatory effect of doxycycline ameliorates systemic and pulmonary inflammation in a Murine polymicrobial sepsis model. *Inflammation* 2020;43(3):1035–43.
- [17] Timani KA, Liao Q, Ye L, Zeng Y, Liu J, Zheng Y, et al. Nuclear/nucleolar localization properties of C-terminal nucleocapsid protein of SARS coronavirus. *Virus Res* 2005;114(1–2):23–34.
- [18] Hiscox JA, Wurm T, Wilson L, Britton P, Cavanagh D, Brooks G. The coronavirus infectious bronchitis virus nucleoprotein localizes to the nucleolus. *J Virol* 2001;75(1):506–12.
- [19] Wulan WN, Heydet D, Walker EJ, Gahan ME, Ghildyal R. Nucleocytoplasmic transport of nucleocapsid proteins of enveloped RNA viruses. *Front Microbiol* 2015;6:553.

- [20] Rizzo E. Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. *Naunyn-Schmiedeberg's Arch Pharmacol* 2020;393(7):1153–6.
- [21] Maurya DK. A combination of Ivermectin and doxycycline possibly blocks the viral entry and modulate the innate immune response in COVID-19 patients. *ChemRxiv* 2020. <https://doi.org/10.26434/chemrxiv.12630539>
- [22] Pandey S, Pathak SK, Pandey A, Salunke AA, Chawla J, Sharma A, et al. Ivermectin in COVID-19: What do we know? *Diabetes Metab Syndr* 2020;14(6):1921–2.
- [23] Gupta D, Sahoo AK, Singh A. Ivermectin: potential candidate for the treatment of Covid 19. *Braz J Infect Dis: Publ Braz Soc Infect Dis* 2020;24(4):369–71.
- [24] Holmes NE, Charles PGP. Safety and efficacy review of doxycycline. *Clin Med Ther* 2009;1:52035. (CMT).
- [25] Gendrot M, Andreani J, Jardot P, Hutter S, Delandre O, Boxberger M, et al. In vitro antiviral activity of doxycycline against SARS-CoV-2. *Mol (Basel, Switz)* 2020;25(21):5064.
- [26] Rothan HA, Bahrani H, Mohamed Z, Teoh TC, Shankar EM, Rahman NA, et al. A combination of doxycycline and ribavirin alleviated Chikungunya infection. *PLoS One* 2015;10(5):e0126360.
- [27] Rothan HA, Mohamed Z, Paydar M, Rahman NA, Yusuf R. Inhibitory effect of doxycycline against dengue virus replication in vitro. *Arch Virol* 2014;159(4):711–8.
- [28] Yates PA, Newman SA, Oshry LJ, Glassman RH, Leone AM, Reichel E. Doxycycline treatment of high-risk COVID-19-positive patients with comorbid pulmonary disease. *Ther Adv Respir Dis* 2020;14. 1753466620951053.
- [29] Ng HH, Narasaraju T, Phoon MC, Sim MK, Seet JE, Chow VT. Doxycycline treatment attenuates acute lung injury in mice infected with virulent influenza H3N2 virus: involvement of matrix metalloproteinases. *Exp Mol Pathol* 2012;92(3):287–95.
- [30] Alam MM, Mahmud S, Rahman MM, Simpson J, Aggarwal S, Ahmed Z. Clinical outcomes of early treatment with doxycycline for 89 high-risk COVID-19 patients in long-term care facilities in New York. *Cureus* 2020;12(8):e9658.
- [31] Glette J, Sandberg S, Hopen G, Solberg CO. Influence of tetracyclines on human polymorphonuclear leukocyte function. *Antimicrob Agents Chemother* 1984;25(3):354–7.
- [32] Santa-Cecilia FV, Socias B, Ouidja MO, Sepulveda-Diaz JE, Acuña L, Silva RL, et al. Doxycycline suppresses microglial activation by inhibiting the p38 MAPK and NF- $\kappa$ B signaling pathways. *Neurotox Res* 2016;29(4):447–59.
- [33] Fredeking TM, Zavala-Castro JE, González-Martínez P, Moguel-Rodríguez W, Sanchez EC, Foster MJ, et al. Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels. *Recent Pat Anti-Infect Drug Discov* 2015;10(1):51–8.
- [34] Castro JEZ, Vado-Solis I, Perez-Osorio C, Fredeking TM. Modulation of cytokine and cytokine receptor/antagonist by treatment with doxycycline and tetracycline in patients with dengue fever. *Clin Dev Immunol* 2011;2011:370872.
- [35] Krakauer T, Buckley M. Doxycycline is anti-inflammatory and inhibits staphylococcal exotoxin-induced cytokines and chemokines. *Antimicrob Agents Chemother* 2003;47(11):3630–3.
- [36] Varisco BM. The pharmacology of acute lung injury in sepsis. *Adv Pharmacol Sci* 2011;2011:254619.
- [37] Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006;54(2):258–65.
- [38] Esterly NB, Koransky JS, Furey NL, Trevisan M. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. *Arch Dermatol* 1984;120(10):1308–13.
- [39] Gabler WL, Tsukuda N. The influence of divalent cations and doxycycline on iodoacetamide-inhibitable leukocyte adherence. *Res Commun Chem Pathol Pharmacol* 1991;74(2):131–40.
- [40] Pruzanski W, Greenwald RA, Street LP, Lauberte F, Stefanski E, Vadas P. Inhibition of the enzymatic activity of phospholipases A2 by minocycline and doxycycline. *Biochem Pharmacol* 1992;44(6):1165–70.
- [41] Ataie-Kachoe P, Badar S, Morris DL, Pourgholami MH. Minocycline targets the NF- $\kappa$ B Nexus through suppression of TGF- $\beta$ 1-TAK1-I $\kappa$ B signaling in ovarian cancer. *Mol Cancer Res: MCR* 2013;11(10):1279–91.
- [42] Mosquera-Sulbaran JA, Hernández-Fonseca H. Tetracycline and viruses: a possible treatment for COVID-19? *Arch Virol* 2021;166(1):1–7.
- [43] Griffin MO, Fricovsky E, Ceballos G, Villarreal F. Tetracyclines: a pleiotropic family of compounds with promising therapeutic properties. Review of the literature. *Am J Physiol Cell Physiol* 2010;299(3):C539–48.
- [44] Ueland T, Holter JC, Holten AR, Müller KE, Lind A, Bekken GK, et al. Distinct and early increase in circulating MMP-9 in COVID-19 patients with respiratory failure. *J Infect* 2020;81(3):e41–3.
- [45] Vanlaere I, Libert C. Matrix metalloproteinases as drug targets in infections caused by gram-negative bacteria and in septic shock. *Clin Microbiol Rev* 2009;22(2):224–39.
- [46] Solun B, Shoefeld Y. Inhibition of metalloproteinases in therapy for severe lung injury due to COVID-19. *Med Drug Discov* 2020;7(100052):100052.
- [47] Gralinski LE, Bankhead III A, Jeng S, Menachery VD, Proll S, Belisle SE, et al. Mechanisms of severe acute respiratory syndrome Coronavirus-induced acute lung injury. *MBio* 2013;4(4). <https://doi.org/10.1128/mbio.00271-13>
- [48] Idell S, James KK, Levin EG, Schwartz BS, Manchanda N, Maunder RJ, et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. *J Clin Investig* 1989;84(2):695–705.
- [49] Dang CV, Bell WR, Kaiser D, Wong A. Disorganization Cult Vasc Endothel Cell monolayers fibrinogen *Fragm D Sci (N Y, N Y)* 1985;227(4693):1487–90.
- [50] Hardy E, Fernandez-Patron C. Targeting MMP-regulation of inflammation to increase metabolic tolerance to COVID-19 pathologies: A hypothesis. *Biomolecules* 2021;11(3):390.
- [51] Klok FA, Kruij MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–7.
- [52] Hountondji C, Besnainou G, Gaudet E, Poupaert JH. Repositioning adequate antibiotics to treat/cure the Coronavirus Disease 2019 (COVID-19): Current treatments and future directions. *Open Biochem J* 2021;15(1):1–19.
- [53] te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* 2010;6(11):e1001176.
- [54] Alirezaei M, Nairn AC, Glowinski J, Prémont J, Marin P. Zinc inhibits protein synthesis in neurons: Potential role of phosphorylation of translation initiation factor-2 $\alpha$ . *J Biol Chem* 1999;274(45):32433–8.
- [55] Lazarczyk M, Favre M. Role of Zn<sup>2+</sup> ions in host-virus interactions. *J Virol* 2008;82(23):11486–94.
- [56] Al-Bari MAA. Targeting endosomal acidification by chloroquine analogues as a promising strategy for the treatment of emerging viral diseases. *Pharmacol Res Perspect* 2017;5(1):e00293.
- [57] Wu Z-C, Wang X, Wei J-C, Li B-B, Shao D-H, Li Y-M, et al. Antiviral activity of doxycycline against vesicular stomatitis virus in vitro. *FEMS Microbiol Lett* 2015;362(22). fmv195.
- [58] An Outpatient Clinical Trial Using Ivermectin and Doxycycline in COVID-19 Positive Patients at High Risk to Prevent COVID-19 Related Hospitalization. (n.d.). *Clinicaltrials.gov*. Retrieved February 22, 2022, from (<https://clinicaltrials.gov/ct2/show/NCT04729140>).
- [59] Clinical Trial of Ivermectin Plus Doxycycline for the Treatment of Confirmed Covid-19 Infection. (n.d.). *Clinicaltrials.gov*. Retrieved February 22, 2022, from (<https://clinicaltrials.gov/ct2/show/results/NCT04523831>).
- [60] Effectiveness of Ivermectin and Doxycycline on COVID-19 Patients. (n.d.). *Clinicaltrials.gov*. Retrieved February 22, 2022, from (<https://clinicaltrials.gov/ct2/show/NCT04591600>).
- [61] Efficacy and Safety of Ivermectin and Doxycycline in Combination or IVE Alone in Patients With COVID-19 Infection. (n.d.). *Clinicaltrials.gov*. Retrieved February 22, 2022, from (<https://www.clinicaltrials.gov/ct2/show/NCT04407130>).