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Therapeutic Potential for Tetracyclines in the Treatment of COVID-19

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Currently there is a race against time to identify prophylactic and therapeutic treatments against COVID-19. Until these treatments are developed, tested and mass produced, it might be prudent to look into existing therapies that could be effective against this virus.

Based on the available evidence we believe that tetracyclines may be effective agents in the treatment of COVID-19. Tetracyclines (e.g. tetracycline, doxycycline, and minocycline) are highly lipophilic antibiotics that are known to chelate zinc compounds on matrix metalloproteinases (MMPs)[1]. Coronaviruses are also known to heavily rely on host MMPs for survival, cell infiltration, cell to cell adhesion, and replication, many of which have zinc as part of their MMP complex[2,3]. It is possible that the zinc chelating properties of tetracyclines may also aid in inhibiting COVID-19 infection in humans limiting their ability to replicate within the host. Tetracyclines might be also able to inhibit RNA replication on positive-sense single stranded RNA, like COVID-19. For example, one study deduced a mechanism discerning how doxycycline could potentially treat the dengue virus. They also showed that at normal human body temperature and fever conditions, doxycycline significantly inhibited the virus' own serine protease as well as noting a concentration dependent decrease in viral replication[4]. They also found that doxycycline inhibited the post infection replication in addition to reducing the viruses' ability to enter the cultured cells[4]. Another study showed that retroviral load was decreased by 70% when cells were treated with the doxycycline at human body temperature[5].

Second, tetracyclines may be able to treat COVID-19 infection through their well-known anti-inflammatory capabilities, including downregulation of the NFKB pathway as well as a decrease in levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 independent of its antibiotic mechanism[6]. It has been shown that these cytokines are significantly elevated when SARS-CoV is exposed to lung tissue in addition to exacerbating the pathogenesis of the infection itself[7]. Furthermore, a recent publication indicated that coronaviruses, irrespective of the species of coronavirus, induces the proliferation of mast cells within the respiratory submucosa, which in turn

produces inflammatory agents such as histamine and protease in addition to inflammatory cytokines such as IL-1 and IL-33[8]. Two other studies showed that chemically modified tetracyclines can induce apoptosis of mast cells and activation of protein-kinase C, thus decreasing levels of circulating inflammatory agents[9,10]. All three groups of investigators suggested that tetracyclines can be used to treat inflammatory disorders, including that induced by coronaviruses[8-10]. It is also worth noting that due to their anti-inflammatory capabilities, tetracyclines have also been documented to have the potential to treat other viral infections such as HIV, West Nile Virus, and viral encephalitis[11].

Third, it is well known that the COVID-19 virus has a lipophilic outer shell. Tetracyclines' lipophilic nature and high tissue penetration in the lungs might allow them inhibit viral replication in the lungs and along with their anti-inflammatory activity, play an important role as therapeutic agents in the treatment of COVID-19. Given that a significant number of patients infected with COVID-19 develop complicated pneumonia or acute respiratory distress syndrome (ARDS), it is possible that tetracyclines might alleviate hospital load and decrease death due to these complications. The recommendation of using tetracyclines as treatment for coronaviruses such as SARSr-CoV has previously been suggested given that chemically modified tetracyclines can prevent septic shock induced by acute respiratory distress syndrome[12].

We believe that tetracyclines can be potential therapeutic agents for COVID-19 that is hiding in plain sight. Moreover, tetracyclines overall are much safer agents than other potential agents that have been considered to treat COVID-19, such as chloroquine or antiretroviral drugs. We strongly urge international research groups to consider investigating the potential therapeutic efficacy of tetracycline antibiotics in treating COVID-19.

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