PHARMACOTHERAPY

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 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 rely heavily 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 also be 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's own serine protease as well as noting a concentration-dependent decrease in viral replication.[4] They also found that doxycycline inhibited the postinfection replication in addition to reducing the virus's ability to enter the cultured cells.[4] Another study showed that retroviral load was decreased by 70% when cells were treated with doxycycline at human body temperature.[5]

Second, tetracyclines may be able to treat COVID-19 infection through their well-known antiinflammatory capabilities including downregulation of the nuclear factor–κ B pathway as well as a decrease in levels of inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 independent of its antibiotic mechanism.[6] It was shown that these cytokines are significantly elevated when the severe acute respiratory syndrome–associated coronavirus (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, induce 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

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inflammatory disorders including that induced by coronaviruses.[8–10] It is also worth noting that due to their antiinflammatory capabilities, tetracyclines were also documented to have the potential to treat other viral infections such as human immunodeficiency virus, West Nile virus, and viral encephalitis.[11]

Third, it is well known that the COVID-19 virus has a lipophilic outer shell. The lipophilic nature and high tissue penetration in the lungs of the tetracyclines might allow them to inhibit viral replication in the lungs and, along with their antiinflammatory 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), 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 was previously suggested, given that chemically modified tetracyclines can prevent septic shock induced by ARDS.[12]

We believe 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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