



Tetracycline and viruses: a possible treatment for COVID-19?

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Abstract

Tetracyclines have been used to treat many bacterial infections. The use of these antibiotics for the treatment of viral diseases dates to the 1960s to 1970s. Over the decades, the effect of tetracyclines on the pathogenesis of viral infections has been demonstrated both clinically and experimentally. Tetracyclines can act on viral infections either through their antibacterial properties or through direct antiviral action. This review focuses on clinical and experimental data that support the use of tetracycline in treating viral infections and highlights an important approach to slowing disease progression during viral infections. Tetracycline treatment might represent a strategy for eliminating the infection or inhibiting the progression of COVID-19.

Introduction

Tetracyclines are broad-spectrum antibiotics [1] that are synthesized by modifying natural tetracycline to form several new compounds. Among these compounds, called semi-synthetic tetracyclines, are doxycycline (Dox) and minocycline (Min). Minocycline (a second-generation tetracycline) acts on Gram-negative and Gram-positive bacteria and is used to treat various types of infections (respiratory tract, skin, urethritis, gonorrhoea, anthrax, meningococcal infections, and chlamydial infections) [2, 3]. The size of minocycline (495 Da) and its lipophilic nature allow it to cross the blood-brain barrier more easily than doxycycline and other tetracyclines [4, 5]. Therefore, it has been used to treat various neurological disorders [6–9]. Doxycycline also has a wide range of antimicrobial [10, 11] and anti-inflammatory [12,

13] properties and is used to treat a variety of infections (anthrax, chlamydial infections, pneumonia, Lyme disease, cholera, syphilis, and others) [14]. The use of tetracyclines as antiviral agents dates to the 1960s and 1970s, and over the decades, they have shown an antiviral effect both experimentally and clinically. The aim of this review was to report on the different antiviral effects of tetracyclines and to highlight their possible beneficial effect on the treatment of COVID-19. In this regard, a literature review was performed. Published studies were identified through citation chasing, a search of PubMed and Google Scholar using the systematic review methods filter, and the authors' topical knowledge.

Effects and properties of tetracyclines

Tetracyclines act through their binding to the bacterial ribosome at high- and low-affinity sites (30S and 50S) and blocking protein synthesis [15, 16]. Allosteric binding of tetracyclines to the ribosome inhibits the binding of aminoacyl-tRNAs at the acceptor site, thus inhibiting protein synthesis [17].

Tetracyclines have other properties besides their antibacterial activity. These antibiotics can inhibit metalloproteinase (MMP) endopeptidases, which are zinc-dependent enzymes that are important in several physiological and pathological processes, including embryogenesis, tissue remodeling, inflammation, and the metastatic action of tumors [18–20]. The mechanism of action of tetracyclines on MMP is not known; however, it has been suggested that

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they have a direct action on metalloproteinase, preventing its expression [21].

Tetracyclines also can act on reactive oxygen species (ROS). The increase in ROS induces oxidative stress during pathological conditions that can lead to the destruction or dysfunction of various cellular components. Reactive oxygen species are formed by the superoxide anion (O_2^-), the hydroxyl radical (OH^-), the non-free-radical hydrogen peroxide (H_2O_2), hypochlorite ($HOCl$), and peroxynitrite ($ONOO^-$) [22]. Dox, Min, and other tetracyclines have a phenolic ring, which can bind to these radicals and eliminate them, leaving a stable, non-reactive phenolic radical [23].

Tetracyclines also have antiapoptotic effects. Caspases are a family of cysteine proteases that activate the apoptosis cascade. After activation of initiator caspases, downstream executioner caspase activation takes place, leading to cellular destruction (apoptosis). Activation of caspases can occur either by external stimulation (death receptor) or by internal stimulation (mitochondrial). Ligands such as TNF- α and Fas, after interaction with cell surface receptor, induce a signal transduction cascade leading to caspase-8 activation, which activates caspase-3. In the intrinsic pathway, the mitochondria are stimulated by internal and external stimuli leading to mitochondrial alterations and resulting in the release of pro-apoptotic factors. These mitochondrial alterations are represented by increased mitochondrial permeability with water influx, inducing mitochondrial swelling and outflow of pro-apoptotic factors such as cytochrome C, Smac/DIABLO, and apoptosis-inducing factor (AIF). These factors activate caspase-9 (cytochrome C), inhibit caspase inhibitors (Smac/DIABLO), and induce DNA fragmentation (AIF). The induction of apoptosis by mitochondria is regulated by pro-apoptotic (Bax, Bad, Bid) and anti-apoptotic (Bcl-2, Bcl-xL) proteins. In these ways, the sequential activation of caspases induces apoptosis [24–26]. Due to their

antiapoptotic action, both Min and Dox have a protective role in various neurological disorders. This neuroprotection is related to a reduction in the expression of caspase-1 and/or caspase-3 [27–30]. Min also acts by inhibiting the mitochondrial release of cytochrome C, Smac/DIABLO, and AIF in cell culture and in a mouse model of Huntington's disease [31]. In this regard, the anti-apoptotic capacity of Min and Dox is demonstrated by their ability to inhibit caspases and induce mitochondrial stabilization [21] (Fig. 1).

Another property of tetracyclines is their potential anti-inflammatory capability. Tetracyclines can be anti-proteolytic agents and ROS inhibitors and are therefore likely to exert an anti-inflammatory effect. Tetracyclines are associated with inhibition of pro-inflammatory cytokines, and MMP and ROS levels, and both Min and Dox can inhibit enzymes such as pancreatic and non-pancreatic phospholipase A2, which are involved in inflammatory processes [32]. Leukocyte migration is critical for inflammatory processes to occur. Tetracyclines can inhibit neutrophil migration [33], as well as leukocyte adhesion [34] and lymphocyte proliferation [35]. Many of the anti-inflammatory effects of tetracyclines are related to their ability to inhibit the functions of the NF- κ B transcription factor. In this regard, Min and Dox inhibit I κ B α (IKK) activation, I κ B α phosphorylation and degradation and p65 and nuclear translocation of NF- κ B [36, 37]. However, other pathways, such as the p38 and ERK1/2/MAPK pathways, can be modulated by the anti-inflammatory effects of Min and Dox [37] (Fig. 2).

Tetracyclines as antiviral agents

The study of tetracyclines as antiviral agents opens an interesting field in microbiological therapy. The first available report on the antiviral activity of tetracycline came when

Fig. 1 Anti-apoptotic properties of minocycline (Min), which has the potential to suppress apoptotic signals in cells. By acting on the extrinsic pathway of apoptosis activation, Min can inhibit the activation of caspase-7, a caspase with pro-apoptotic activity. In the intrinsic pathway of apoptosis activation, Min can inhibit oligomerization of pro-apoptotic mitochondrial proteins (Bax/Bak) and the export of cytochrome C and Smac/Diablo, blocking activation of caspase 9 and its effect on caspase 3 activation. Min also blocks the apoptotic effect of caspase 3

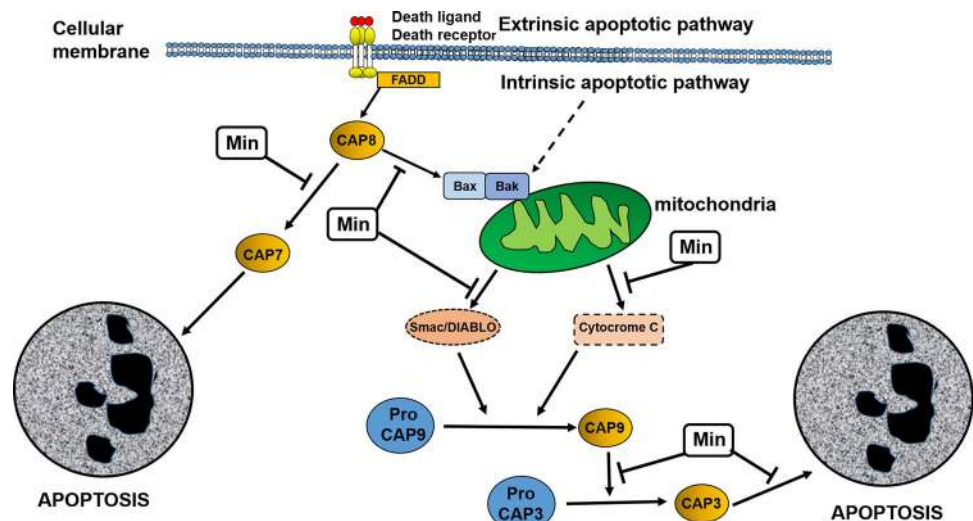
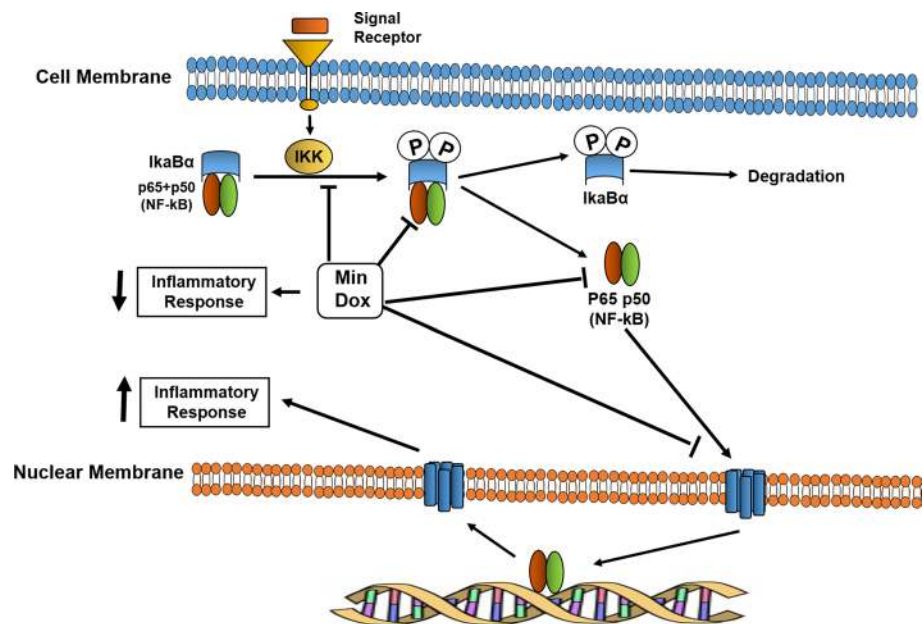


Fig. 2 Effect of tetracyclines on the NF- κ B transcription factor pathway. Minocycline (Min) and doxycycline (Dox) are capable of inhibiting the NF- κ B pathway, acting on different points of this activation by inhibiting I κ B α (IKK) activation, I κ B α phosphorylation, degradation and p65, and nuclear translocation of NF- κ B, leading to a decreased pro-inflammatory immune response



Negrette et al. reported, between 1960 and 1970, that tetracyclines provide protection against several viruses. In this regard, clinical experience demonstrated the beneficial role of tetracycline in epidemics of Venezuelan equine encephalitis (VEE) virus and infectious mononucleosis (Maracaibo, Venezuela), as well as in other viral conditions [38–44]. Tetracyclines also showed a high protective effect in mice and chicken embryos infected by VEE virus [45, 46]. These findings were reported at a time when the use of antibiotics for the treatment of viral diseases was unknown.

In recent decades, Min and Dox and other tetracycline compounds have been extensively studied for their antiviral activity. Lemaitre et al [47] reported that Min and Dox had a protective effect against the human immunodeficiency virus (HIV) by preventing the cytopathic effects of the virus on human lymphoblastic T cells. Other studies showed that inhibition of the microglia by Min in cell culture reduced the production of HIV by those cells [48]. In a simian immunodeficiency virus (SIV) model, Min reduced the severity of encephalitis, brain viral load, and expression of brain inflammatory markers. In addition, Min inhibited SIV replication *in vitro* [49]. These protective effects were mediated by suppression of p38MAPK and JNK levels in the brain, which inhibit the kinase-regulated apoptosis signal (ASK1) [50]. In addition, Min has affinity for HIV-1 integrase [51], inhibiting the integration of viral DNA into the host genome.

Min is also effective against flavivirus infections. This antibiotic inhibited West Nile virus (WNV) replication in cultured human neural cells, preventing virus-induced apoptosis [52]. In experimental infection with Japanese encephalitis virus (JEV) in mice, Min reduced neuronal apoptosis, microglial activation, caspase activation, production of brain

proinflammatory mediators, and viral replication [53]. Macrophage migration inhibitory factor (MIF) facilitates dengue virus replication by inducing autophagy. Treatment with Min decreased the viral load, MIF secretion, and autophagy, and increased survival in dengue-virus-infected mice [54]. In other studies, Min was shown to induce the expression of genes associated with anti-inflammatory activation (M2) in the microglia while it inhibited the expression of genes associated with pro-inflammatory activation (M1) in WNV-infected mice, reducing cytotoxicity in response to WNV [55]. Min also confers protection against alphavirus infection in animal models by inhibiting microglial activation and decreasing production of interleukin-1-beta in the central nervous system [56]. In VEE virus-infected mice, Min decreased viral replication, nitric oxide production, and lipid peroxidation in the brain and in cultures of virus-infected neuroblastoma [57]. Min reduced the cytopathic effect mediated by respiratory syncytial virus and prevented infection by this virus [58]. Min is an antiviral agent in mice infected by enterovirus 71, reducing the expression of cytokines and viral replication. In addition, Min reduced the cytopathic effect in THP-1 cell cultures infected with enterovirus 71 [59]. Crimean-Congo hemorrhagic fever virus is a member of a family of hemorrhagic fever viruses, and its nucleoprotein is a key protein in virus replication. Min and Dox can inhibit this protein, slowing viral replication [60].

Dox has also shown antiviral activity. Recent studies have demonstrated the importance of the p53 protein in the host antiviral response against several viruses, including vesicular stomatitis virus (VSV) [61] and influenza virus [62]. The ability of Dox to induce p53 probably extends the antiviral effect of this antibiotic. In this regard, the inhibition of p53

expression by JEV in H1299 cell cultures was inhibited by Dox [63, 64]. Dox also inhibited the cytopathic effect and viral replication in H1299 cell cultures infected by VSV [64]. This antibiotic significantly reduced the cytopathic effect and viral replication in Marc-145 cells infected by swine respiratory syndrome virus [65]. Dox also reduced the severity of acute lung injury in mice infected with influenza H3N2 virus [66]. The antiviral effect of Dox against flaviviruses has also been reported. *In vitro* studies have shown that Dox prevents the entry and replication of chikungunya virus in Vero cell cultures [67]. Dox also inhibited the serine protease of dengue virus (DENV NS2B-NS3pro), inhibiting the entry and replication of four dengue serotypes (DENV2, DENV4, DENV1 and DENV3) in Vero cell cultures [68, 69]. In addition to this mechanism, Dox, through its tetracyclic rings, can alter the conformation of the dengue virus envelope protein and block the entry of this virus into the cells [70] (Fig. 3).

Viral resistance to tetracycline could be a problem in tetracycline treatment. Antibiotic resistance occurs when germs like bacteria and fungi develop the ability to defeat the drugs designed to kill them. Tetracycline resistance is widespread among Gram-positive and Gram-negative bacteria and can be the result of pumping the drug out of the cell before it reaches its site of action (efflux), protection of the ribosomal

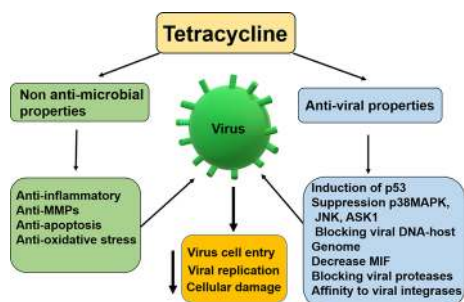
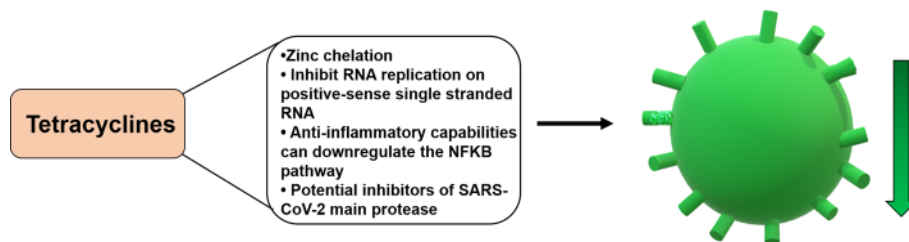


Fig. 3 Effect of tetracyclines on viral pathogenesis. Tetracyclines can affect the viral life cycle by indirect and direct mechanisms. Indirect effects are based on anti-apoptotic, anti-metalloproteinase (MMPs), anti-oxidative stress, and anti-inflammatory properties of these compounds. Different mechanisms of antiviral activity of tetracyclines have been reported. Overall, the properties of tetracycline by acting on viral pathogenesis leads to decreased entry of the virus into the host cell, decreasing its replication and cellular damage. MIF, macrophage inhibitory factor

Fig. 4 Potential effects of tetracyclines on SARS-CoV-2. Several properties of tetracyclines can potentially decrease the ability of SARS-CoV-2 to enter and reproduce in the cell



binding site, which decreases drug binding, or changes in the permeability of the cell envelope that reduce drug uptake [71]. Viruses are not living particles; they need host cells to replicate. The antiviral effect of tetracyclines is indirect and involves several mechanisms that the viruses use to enter and replicate cells. The blockage of protein synthesis in the cell by tetracyclines might inhibit virion formation. Thus, it is unlikely that the mechanisms of antibiotic resistance used by viruses will be similar to those used by bacteria is unlikely.

COVID-19 and tetracyclines

A new severe acute respiratory syndrome coronavirus (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, in December 2019 [1]. Currently there is a race against time to identify therapeutic treatments for COVID-19. SARS-CoV-2 is a new emerging zoonotic coronavirus belonging to the same viral family as the viruses that cause SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome). Tetracyclines (e.g., tetracycline, halogenated tetracyclines, doxycycline, and minocycline) are highly lipophilic antibiotics that are known to chelate zinc compounds on matrix metalloproteinases (MMPs). Several functions of coronavirus are associated with the host MMPs complex, including replication [72, 73]. Therefore, the zinc-chelating properties of tetracyclines may also aid in inhibiting SARS-CoV-2 infections in humans, limiting their ability to replicate within the host. Tetracyclines might also be able to inhibit RNA replication of positive-sense single-stranded RNA viruses [69], like SARS-CoV-2, and they can downregulate the NF- κ B pathway, decreasing the levels of inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 induced by SARS-CoV-2. In addition, tetracyclines stand out as potential inhibitors of the main protease of SARS-CoV-2 [74] (Fig. 4). In this context, various investigators have suggested the use of tetracyclines as potential therapeutic agents for the treatment of COVID-19 [74–76].

The effect of tetracyclines on apoptosis in relation to their antiviral activity may be controversial in the context the virus type and the stage of cellular infection. As described above, tetracyclines can inhibit apoptosis but they can also induce apoptosis [77, 78]. A interesting point regarding

apoptosis is that a cell invaded by a virus needs to be eliminated by the organism as an infected cell, using various mechanisms, including the antiviral immune response [79], but the virus requires a living cell for reproduction, and in the late period of infection can use apoptosis as a means of breaking the cell and increasing the spread of the virus [79]. Therefore, the antiviral effect of tetracyclines on apoptosis may be related to the spread of infection. When tetracyclines induce apoptosis [77, 78], they can favor the dissemination of the virus, but at the same time decrease its replication, but when tetracyclines block apoptosis [27–31], they can decrease spread of the virus. It has been reported that SARS-CoV-2 induces apoptosis in infected cells [80], and the effect on this process of tetracycline remains unknown.

Although several studies have shown that tetracyclines have antiviral and anti-inflammatory effects, all of them have been *in vitro* studies using experimental models. There are still no final results of clinical studies demonstrating the efficacy of these antibiotics for treatment of patients with COVID-19. There has been only one phase 2 study in which doxycycline was used together with ivermectin for the treatment of COVID-19 patients [81]. However, the potential of tetracyclines as an antiviral drug is high and requires further clinical studies. It is important to develop antiviral treatments for COVID-19 that can be administered early in infection in order to avoid the organ damage caused by the virus and allow the patient to produce a strong immune response against the virus. Therapeutic interventions in patients with severe organ damage caused by the virus or by an excessive immune response may have little effect on eliminating the virus or the recovery of the patient when antiviral strategies are given at later times.

Conclusion

Experimental studies have shown that the antiviral effects of tetracyclines are based on their anti-apoptotic and anti-inflammatory activities and on direct effect on viral biology, leading to inhibition of viral entry and viral replication. These studies highlight an important and fruitful approach in antiviral drug research. The early use of tetracyclines in COVID-19 could have a beneficial effect, preventing the viral infection from progressing to more serious stages that can lead to death in individuals infected with SARS-CoV-2.

Author contributions JM and HHF selected the topic, initiated the project, conceptualized the ideas, and drafted the manuscript. All authors contributed to literature search, analysis, interpretation, and manuscript preparation. All authors have critically reviewed, discussed, and approved all the content of the manuscript for publication.

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Compliance with ethical standard

Conflict of interest No potential conflict of interest is reported by the authors.

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