

# Communication: Novel Drug Combination Doxycycline-Melatonin-Digoxin(D-M-D) for Possible Covid-19 Treatment

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**Abstract:** Covid-19, stands for a Coronavirus disease appeared in Wuhan province of China in December 2019, for first time. So far, it has spread rapidly throughout the world with mortality of 1-2% in general population. The main fatal mechanism is acute respiratory distress syndrome due to the development of severe pneumonia with or without sepsis, especially in patients aged over 50 with serious comorbidities.

The deadly outcome of Covid-19 regarding the aforementioned infected group, has intensified scientific research worldwide in order to create novel vaccination and drug treatment. Based on current Guidelines of National Health Commission of the People's Republic of China drugs such as IFN $\alpha$ , Lopinavir/ritonavir, Ribavirin, Chloroquine phosphate and Arbidol have been proposed for the treatment of Covid-19 infection. Yet, research is still ongoing on a variety of other potential drugs.

Doxycycline(D), is an antimalarial antibiotic which exhibits both anti-inflammatory and antiviral action. In particular, doxycycline inhibits Dengue virus replication *in vitro*.

Melatonin(M), among other mechanisms demonstrates immune-regulatory, antioxidant and antiviral activity, as well. Melatonin administration shows protective action in cases of Acute Respiratory Distress Syndrome(ARDS) and septic shock.

Digoxin(D), is a cardiac glycoside which has been scientifically proven to possess antiviral properties. The main inhibition mechanism is the blocking of Na-K-ATPase in a variety of viral infections, including Coronavirus family's ones.

Hypothesis, that the three previous agents(D-M-D) deserve to be scientifically tested in combination as potential drug treatment against Covid-19, seems to be a well-established proposal.

**Keywords:** Covid-19, Melatonin, Digoxin, Doxycycline, antiviral treatment.

Covid-19-RNA virus, stands for a Coronavirus disease appeared in Wuhan province of China in December 2019, for first time. Due to its highly contagious behavior very fast spread throughout the world and created the 2019-20 Coronavirus pandemic. Common symptoms of the disease include fever, cough and shortness of breath while less commonly symptoms such as sore throat, sputum production, loss of smell-taste, diarrhea, abdominal pain and fatigue may be reported. Almost all ages may be infected. In most cases, the course of the disease is mild and self-cured, nevertheless, for those people over 50 with serious comorbidities, severe pneumonia, sepsis and multi-organ failure may have fatal outcome [1-2]. As of 9<sup>th</sup> of April 2020, over 200 countries have reported approximately 1,107,149 Covid-19 active cases, 89,954 deaths and 340,390 cured patients (world-meter coronavirus pandemic statistics).

High mortality rate amongst Covid-19 compromised patients has led to extensive research worldwide. Over 30 agents have been tested as potential drug therapy.

Certain of these drugs, such as Interferon  $\alpha$  (IFN- $\alpha$ ), lopinavir/ritonavir, chloroquine phosphate, ribavirin, arbidol have been included in the latest version of the Guidelines for the prevention, diagnosis and treatment of Novel Coronavirus-induced pneumonia issued by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of Covid-19 treatment [3]. Yet, intensive investigation is still ongoing on a variety of other potential drugs.

Doxycycline (D) is an antibiotic derived from tetracycline that demonstrates mainly antimicrobial and anti-inflammatory properties. Current research has focused on anti-Dengue-viral behavior of Doxycycline *in vitro*. D significantly inhibited virus serine protease blocking in this way viral entry and post-infection replication of four Dengue serotypes [4]. Moreover, patients seriously infected by the RNA-Dengue virus exhibit high levels of IL-6 and Tumor Necrosis Factor (TNF). Through administration of D, both mortality rate and IL-6, TNF decreased [5]. Additionally, there is a direct proportional link between serum cytokine level and mortality rate, while D seems to modulate Cytokine and cytokine receptor/antagonist effectively [6]. Similarly, in developing ARDS induced by Covid-19 infection, the produced cytokine cascade (i.e. IL-6, IL-7,

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IL-10, TNF- $\alpha$ , G.C.S.F.) accelerates fatal outcome [7]. So, it is very important to find a way to control the overwhelming immune response that destroys alveolar epithelium and leads critically ill patients to irreversible ARDS. D seems to protect lung tissue through modulation of cytokine cascade and possibly prevent the Covid-19 invasion into epithelial human cells.

Melatonin (M) is a hormone distributed ambiguously in human body. In Central Nervous System (CNS) plays an extraordinary role in maintain Circadian rhythm for every day sleep-wake cycle [8]. Additionally, M may be produced and detected in other organs such as thymus, retina, bone marrow, lymphocytes etc. Currently, its implication in immune response mechanisms has drawn significant attention and research interest, alike [9]. The immune-regulatory action of M takes place via antioxidant pathways and inhibition of pro-inflammatory mediators. Also, M seems to ameliorate ARDS and septic shock through its antimicrobial and antiviral properties [10]. Of notice, a recent study in mice dealing with H1N1 influenza A infection, has proven that the administration of M demonstrates an outstanding behavior: the severe pneumonia could be treated via the ability of M to act in cooperation with classic antiviral drug, enhancing in this way its anti-inflammatory and immune-modulatory effects [11]. Taking into consideration the aforementioned data, M likely, could act beneficially in co-administration with other drugs to combat Covid-19 infection.

Digoxin (D), belongs to Cardiac Glycosides (CG) family which operates not only on Na-K pump ATPase by inhibiting its function, but also triggers intracellular pathways which are essential for a variety of biochemical procedures [12]. Currently, CG have been reported to have antiviral action against both DNA (i.e. Cytomegalovirus, herpes simplex) and RNA viruses (i.e. influenza, coronavirus, chikungunya) [13]. It is well known, that influenza demonstrates a significant contagious, acute respiratory syndrome with increased morbidity and mortality. On the other hand, people infected by Coronavirus, causing either middle-east respiratory syndrome (MERS-CoV.) or epidemic severe acute respiratory syndrome (SARS-CoV.) recuperate significantly by the use of CG via inhibition of Na-K-ATPase and Src pathway [13]. Nowadays, scientific community has witnessed a worrying increase of anti-viral drug resistance. CG appear to be very promising novel drugs (in co-administration with anti-viral agents) to combat viral mutations and resistance effectively

[14]. Thus, D may have a role in the fight against the novel disease Covid-19.

In conclusion, although Covid-19 is a new introduced infection, is a serious one, with significant morbidity and mortality especially in immuno-compromised, and those patients with serious comorbidities. Intensive research worldwide aims to develop as fast as possible effective medical tools to handle and suppress the aggressive behavior of Covid-19. In this direction, based on anti-viral action of Doxycycline-Melatonin-Digoxin(D-M-D), the current approach shows promising indications for Covid-19 treatment. Furthermore, it is worth mentioning that D-M-D are well tolerated in their previous applications without significant side effects [15-17]. Yet, preclinical and clinical protocols should be performed in order to verify the potent efficacy of them.

## CONFLICT OF INTEREST

Authors declare that there is no conflict of interest in this study.

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