

# The coronavirus pandemic: could combining melatonin and glycyrrhizin be the solution for this ongoing emergency?

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## Abstract

Novel Corona Virus Disease 2019 (COVID-19) continue to sweep various nations causing more than 4.5 million confirmed cases and close to 300,000 deaths. Current pharmacotherapy largely fall short of controlling the pandemic. In this letter, we critically appraise the hydroxychloroquine plus azithromycin regimen recommended by Gautret et al and provide rationale for new treatments.

## The coronavirus pandemic: could combining melatonin and glycyrrhizin be the solution for this ongoing emergency?

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Confirmed novel coronavirus disease (nCoV or COVID-19), 1<sup>st</sup> reported to the world health organization (WHO) end of last year, evolved since January 30<sup>th</sup> 2020 into an unprecedented worldwide pandemic . As we write, confirmed cases reached more than 1.7 million people with more than 103 thousand deaths globally . We and other believe the observed death percentage of about 21% for cases with final outcome far exceed the reported natural COVID-19 mortality. One major element in this lethal scenario is the fact that COVID-19 is a new emergent strain which is highly infectious and lethal through its modified spike protein. On the other hand, severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock, and multi-organ failure and death occur in about 20 to 30% of cases. Among these approximately about 5% would be in critical condition at any given point in time . These figures already strained even the best healthcare systems known in modern times including those of Europe and North America. Most plausible explanation of this

toxic COVID-19 pandemic progression is the duality of a highly transmittable disease coupled with a massive cytokine storm and exaggerated immune response that a proportion of patients go through .

COVID-19 Vaccine Development Taskforce is working to finance, develop and deploy vaccines with fair global distribution. Additionally, several groups continue to explore several potential host and viral targets to make drug therapy breakthroughs. Pending the design of very specific effective antiviral therapy, clinicians and researchers alike focus their efforts on best re-employment of re-purposed molecules (e.g. melatonin). Remdesivir is probably the most promising antiviral ahead so far. Evidence for hydroxychloroquine  $\pm$  azithromycin is insufficient . Based on this last study, It seems that Azithromycin is crucial for those patients presenting with a lower respiratory tract or lung infection. However, azithromycin has no known antiviral activity and the mechanism by which it produced this positive outcome is probably through its immune modulating and anti-inflammatory effect. Nevertheless, progression persisted (6 cases out of 26) which may be explained by the lower concentration of azithromycin in serum and the central nervous system where significant viral tropism exists. Hence, we should investigate more options in this current surge.

Melatonin is a relatively safe and accessible molecule, now sold over the counter in Jordan and around the world. This is a natural pineal gland hormone which is broadly used in many indications including cardiovascular, neurological and endocrinology. Many studies showed that it assists in eradicating viral infections with multiple positive anti-inflammatory, immune-modulatory, as well as neuro- and other vital organ protective effects. Melatonin interferes with multiple COVID-19 targets, including the angiotensin converting enzyme 2 (ACE 2), it also has anti-oxidative stress, anti-inflammatory and cytokine modulatory effects in sepsis, septic shock, acute respiratory syndrome, and multi-organ failure. It has human cell membrane stabilizing effect which may interfere with viral budding. Melatonin, at a dose of 10 mg or higher (orally or intravenously), reduced a number of markers/cytokines including C-reactive protein and tumor necrosis factor (TNF  $\alpha$ ) and prevented progression to chronic lung disease especially in the setting of sepsis in adult and pediatric populations. For example, it reduced ischemic re-perfusion injury and multi-organ failure in septic patients. Moreover, melatonin can target the potential central nervous system tropism of similar viruses in animal models. We have proposed to our Jordan COVID-19 crisis committee in a letter to Editor of reputable journals a combination of melatonin and ascorbic acid (authors' correspondence). Furthermore, an analysis of the first 12 cases of COVID-19 in the United States revealed that there was one case of a middle-age (i.e. 50 to 59-year-old) man who had bilateral consolidation pneumonia and received as needed melatonin doses. This patient had early signs of multi-organ injury based on high liver enzymes; ALT and AST of 389 and 190 U/L, respectively. Procalcitonin was consistent with a local inflammation at a level of 0.13 ng/ml. All these values persisted at this average for 13 days. In this case, the outcome was eventually clearance of the positive COVID-19 sample in 8 days and hospitalization continued for 7 days only. Further support to this potential adjuvant role of melatonin in COVID-19 infections comes from China itself, as summarized by Zhang and his colleagues.

Glycyrrhizin is a steroid-related chemical structure obtained from licorice root with inhibitory action on oxygen and nitrogen species-mediated lung damage. Nature again presents us with this molecule which has broad spectrum antiviral activity. Glycyrrhizin was more active back in 2003 against the older closest human relative of COVID-19, namely, the severe acute respiratory syndrome coronavirus (SARS CoV) than a variety of medications including ribavirin. It also has protective effects against sepsis, septic shock, acute respiratory distress syndrome and multi-organ injury. Glycyrrhizin follows a dose-independent pharmacokinetics with observed distribution largely confined to the vascular compartment at a dose range of 40 to 120 mg oral daily. In Jordan, there is a local product that contains this ingredient under the brand name Dilamuc Syrup® from Jerash Pharmaceuticals. Usual adult dose is 15 ml divided three times daily (daily dose of 24.6 mg of glycyrrhizin). Friends in the domestic poultry business uses nebulized forms of this molecule to treat various dangerous viral respiratory illnesses including avian flu. Therefore, in this emergent pandemic, we strongly recommend conducting randomized controlled or at least open label trials of adding melatonin and glycyrrhizin protocols to the management of COVID-19 patients with different severity levels. A recommended protocol that can be trialed for COVID-19 crisis is as follows:

- Melatonin: start dose at 10 mg oral stat post first blood level and escalate to a target dose of 5 to 80 mg daily, given 60% in the evening and 40% in the morning based on age and severity.
- Glycyrrhizin: start with 5 ml (8.2 mg) three times daily, escalate to a target dose of 5 to 10 ml (8.2 to 16.4 mg) three times daily.

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