



The therapeutic potential of colchicine in the complications of COVID19. Could the immunometabolic properties of an old and cheap drug help?



A B S T R A C T

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The present study analyzes the importance of the inflammasome that involves the NLRP3 complex in the state of hypercytokinemia observed in patients with COVID-19, significantly increasing IL-1 β , IL18, IL-6, and TNF. Unfortunately, improving the immune response can sometimes worsen the outcome of the disease. Studies show that colchicine, among other actions, inhibits the assembly of NLRP3 complex that is responsible for generating the active form of Caspase-1 that will convert Pro-IL-1 β and Pro-IL-18 into their active forms. We suggest using colchicine, a class of drugs with low-cost, extensively tested, well-tolerated medicine as a complementary treatment for patients with COVID-19, in early stages of the disease based on knowledge of its immunomodulatory properties.

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1. Introduction

The present study analyzes the importance of the inflammasome that involves the NLRP3 complex in hypercytokinemia, present in patients diagnosed with SARS-CoV-2, as well as the metabolic actions of colchicine in inhibiting the activation of this inflammasome by different mechanisms. We also discussed the safety and suggested that it be a therapeutic option for patients in settings where modern immunosuppressants are not available.

2. Production inflammatory cytokine in patients with Sars-Cov-2

We know the innate immune system is non-specific to infectious agents and consists of mechanisms and molecules with a rapid response to infection. One indication that immunopathogenesis may contribute to SARS was the observation that viral load in patients decreased while disease severity increased. Most of these critically ill and dead patients did not develop severe clinical manifestations in the early stages of the disease. In patients with conditions that have deteriorated suddenly in the more advanced stages of the disease or even in the recovery process, it may be due to the positive regulation of pro-inflammatory cytokines [1].

Inflammation is stimulated by chemical factors released by injured cells and serves to establish a physical barrier against the spread of infection and to promote healing of any damaged tissue following the clearance of pathogens. The process of acute inflammation is initiated by cells already present in all tissues. The primary effector cells, which include neutrophils, macrophages, dendritic cells, histiocytes, Kupffer cells, and natural killer (NK) cells, rapidly move to the site of infection or tissue damage and

cause resolution of infection and tissue repair [2,3].

PRRs (Pattern Recognition Receptors) are receptors of the innate immune system that specialize in the recognition of pathogens like bacteria and viruses. PRRs are protein molecules encoded in the human genome and are mainly present on immune cells like macrophages, monocytes, neutrophils, epithelial cells, and dendritic cells.

The PRRs recognize highly conserved structural motif known as Pathogens Associated Microbial Patterns (PAMPs), which are exclusively expressed by microbial pathogens or Danger Associated Molecular Patterns (DAMPs) that are endogenous molecules released from necrotic or dying cells [4] (Fig. 1).

Recognition of microbial products by PRRs leads to a variety of signal transduction pathways that regulate the nature, magnitude, and duration of the inflammatory response [5]. The loss of the ability to monitor the quality or extension of the host's inflammatory response can be detrimental if cascades are not appropriately controlled.

The NLRP3 inflammasome is defined by its sensor protein (a PRR), which oligomerizes to form a pro-caspase-1 activating platform in response to DAMPs or PAMPs [6–10].

Caspase-1 is activated via proximity-induced autocatalytic activation, and now the active caspase-1 cleaves the cytokines pro-interleukin-1 β (pro-IL-1 β) and pro-interleukin-18 (pro-IL-18) into their mature and biologically active forms [12–14]. The production of acute-phase proteins in hepatocytes is controlled by various cytokines released during the inflammatory process. During the hepatic acute phase response, the liver increases the synthesis of specific proteins up to 1000 times, including mediators of the inflammatory processes like C-reactive protein, α 1-acid glycoprotein, haptoglobin, fibrinogen, α 1-antitrypsin, and complement components C3 and C4. All of them will be responsible for several of the

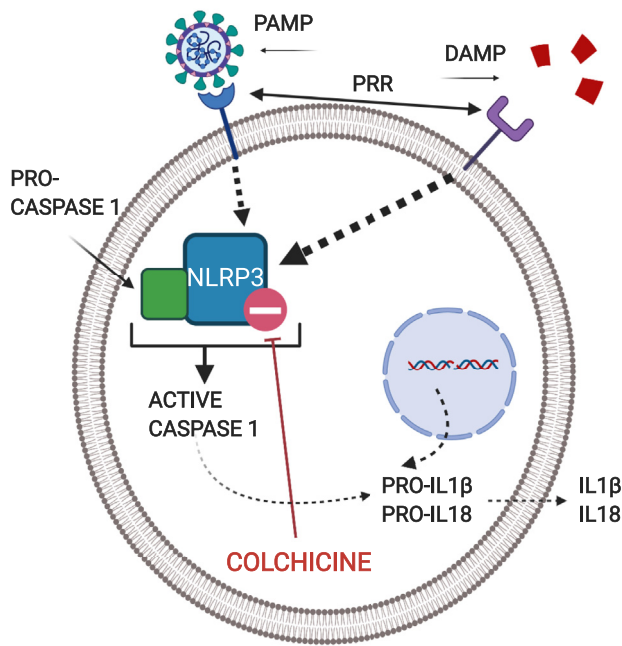


Fig. 1. PRRs are activated by PAMPs or DAMPs, and this causes the NLRP3 inflammasome to become active and convert pro-caspase-1 into caspase-1. Now, Caspase 1 can transform pro-IL-18 and pro-IL-1 β , which have been synthesized in the nucleus into their active forms that are released by exocytosis. **PRRs** - Pattern Recognition Receptors, **PAMP**-Pathogens Associated Microbial Patterns, **DAMP**-Danger Associated Molecular Patterns, **pro-IL-1 β** - pro-interleukin-1 β , **pro-IL-18** - pro-interleukin-18.

clinical manifestations of SARS-CoV-2 [19,20].

The NLRP3 inflammasome is essential for host immune defenses against viral infections, but it has been linked to the pathogenesis of several inflammatory disorders when dysregulated, including Cytokine Storm. The NLRP3 inflammasome also was described as an essential mediator of virus-induced inflammation by a path independent of DAMPs and PAMPs. The perturbation of membrane permeability by Viroporins and subsequent disruption of ions homeostasis in cellular compartments is a possible path for the production of IL-18 and IL-1 β [15–17].

As for COVID-19, studies have reported higher IL-18 and IL-1 β , indicating an increase in the NLRP3 inflammasome activation. Coronavirus has 2 Viroporins: the E protein and the 3a protein, which act as ion-conductive pores in planar lipid bilayers and are required for maximal SARS-CoV-2 replication and virulence. They could also be responsible for Cytokine Storm by inflammasome activation [6,18].

Inflammatory mediators play a vital role in the pathogenesis of ARDS, a primary cause of death in patients infected with SARS-CoV-2 [7]. Several cytokines, including IL-6, IL-8, and IL-1 β , contribute to ARDS [8]. Additionally, uncontrolled epithelial cell proliferation and impaired tissue remodeling during later stages induce ARDS leading to pulmonary fibrosis and death.

Infection with the dengue virus is another viral disease characterized by an exacerbated immune response from the host, which plays an essential role in the development of severe clinical manifestations. This response is marked by the antibody-dependent enhancement (ADE) that occurs when infection by the dengue virus serotype predisposes the person to a more severe disease after secondary infection by the heterologous dengue virus serotype [11].

The ADE was proposed to explain the difference between the severity of the cases observed in Hubei province, China, and those occurring in other parts of the world. One possible answer is the

ADE of SARS-CoV-2 due to previous exposure to other coronaviruses. ADE modulates the immune response and can cause sustained inflammation, lymphopenia, and a cytokine storm, which are well documented in severe cases and death [12].

ADE is a potential risk associated with the development of a vaccine against COVID19 since antibodies that bind to the virus without neutralizing infectivity can cause diseases through increased viral replication or immune complex formation, which deposit in the lung and other organs and activate the pathway associated with inflammatory cytokines.

However, today there is not enough evidence to support that ADE can occur in COVID19. The development of vaccines and the presence of people who have been infected and developed mild forms of infection with COVID19 need to have this potential risk assessed from the beginning.

3. NLRP3 inflammasome and colchicine

Colchicine is an alkaloid extracted from plants of the genus *Colchicum* (autumn crocus) that has been discovered to inhibit many steps in the inflammatory process. Its history as an herbal remedy for joint pain goes back at least to the 1500 BCE Egyptian manuscript, the Ebers Papyrus. The drug has good oral bioavailability. Toxicities are primarily gastrointestinal, hepatic, and hematologic.

The therapeutic use of colchicine has been well documented in gout and Familial Mediterranean Fever (FMF); it has also been used in other diseases including Behcet's disease (BD), pericarditis, coronary artery disease, primary biliary cirrhosis, psoriasis, aphthous stomatitis, linear IgA dermatosis, relapsing polychondritis, Sweet's syndrome, scleroderma, amyloidosis, leukocytoclastic vasculitis, epidermolysis bullosa, and dermatomyositis, idiopathic retroperitoneal fibrosis and other inflammatory and fibrotic conditions [22–24].

The colchicine can decrease the expression of the TNF- α receptor in macrophages and reduce cytokines IL-1 β , IFN γ , IL-18, and IL-6. Over the years, many studies have shown its therapeutic potential for various inflammatory conditions [25–27].

Colchicine suppresses NLRP3 inflammasome, but the mechanism is still unknown. It could be related to the disruption of microtubule-dependent transport of mitochondria to the endoplasmic reticulum. The assembly of NLRP3 in the endoplasmic reticulum with its adaptor is required to activate the inflammasomes [28–30] (Fig. 1).

Colchicine showed to modulate the lipopolysaccharide-induced secretion of tumor necrosis factor (TNF) by liver macrophages in a rat model. In the presence of colchicine, macrophages showed less reactive oxygen species formation, nitric oxide, and IL1 β release. After colchicine treatment, mice inoculated with lipopolysaccharide, and ATP had diminished ROS, IL1 β , interferon- γ , and NO production [18,31].

Pathological studies have reported that patients infected with COVID-19 can develop consolidation in the lungs by fibroblast proliferation in the alveolar air spaces [32]. The colchicine has anti-fibrotic effects as a microtubule-destabilizing agent. We know that myofibroblast differentiation plays a critical role in wound healing and the pathogenesis of fibrosis. In an in vitro study using human lung fibroblasts, colchicine inhibited myofibroblast differentiation via Rho/serum response factor (SRF) dependent [31–33].

The cardiovascular applications of colchicine have been evolving in the last decade. Colchicine was shown to have synergistic protective effects with atorvastatin on endothelial function, reduced C-reactive protein (CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and enhanced NO production in rats [34]. Colchicine has also been shown to affect the expression of adhesion molecules on endothelial cells, leukocytes, and to decrease activation of

thrombin-induced platelet aggregation [35], for this reason, have been used to prevent deleterious effect on coronary arteries induced by radiation therapy by inhibiting inflammation and platelet aggregation. The short-term study also demonstrated that the colchicine administration rapidly and significantly reduces local cardiac production of the inflammatory cytokines (IL-1 β , IL-18, and IL-6) in patients with acute coronary syndromes [36].

The efficacy and safety of colchicine for the primary prevention of the postpericardiotomy syndrome (PPS), postoperative effusions, and postoperative atrial fibrillation (POAF) have been shown in the colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial [37]. Based on early observational experiments, the European Society of Cardiology has recommended colchicine as a treatment option for pericarditis and post-pericardiotomy syndrome (level of evidence B, class IIa), either as an adjunct to NSAIDs or as monotherapy [38].

A recent large randomized, double-blinded study with 532 subjects who had coronary artery disease and who took colchicine 0.5mg daily for a median of three years, demonstrated a reduction in the incidence of acute cardiovascular events, or non-hospital cardiac arrests or non-cardioembolic ischaemic strokes in the colchicine treatment arm (5.3% vs. 16% $p < 0.001$) [39].

Colchicine has been the treatment of choice for Familial Mediterranean Fever (FMF) since the 1970s. There are several long-term follow-up studies, including one longitudinal study, in which patients taking colchicine for a minimum of 15 years showed the safety and efficacy of this therapy.

Colchicine has a narrow therapeutic window. When prescribed daily and chronically for FMF, the most common adverse reactions are abdominal pain, diarrhea, nausea, and vomiting. These effects are usually mild, transient, and reversible upon lowering the dose. Prescribed for gout attacks with doses up to 1.8 mg, the most common adverse reaction is diarrhea (23%). However, therapeutic doses of colchicine can lead to blood dyscrasias, including myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia [40].

Colchicine is a substrate for intestinal and hepatic cytochrome CYP3A4 and a substrate for P-glycoprotein (P-GP) [37]. Fatal drug interactions have been reported in patients treated with colchicine and concomitant P-GP inhibitors (e.g., cyclosporine and ranolazine) or potent CYP3A4 inhibitors (e.g., clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, and some protease inhibitors) [41]. We have to avoid using colchicine with drugs that can increase its toxicity. Dose reductions in colchicine should be considered in patients with renal or hepatic impairment and the elderly. Some recommendations suggest reducing the dose of colchicine by 50% in patients with creatinine clearance below 50 ml/minute [42].

Our research looked for the interaction of colchicine with drugs commonly used in patients with SARS-CoV-2 that were not described in the previous paragraph. We need to assess whether the patient is using medications that increase the risk of adverse events due to an interaction with drugs that inhibit CYP3A4 or P-GP [43].

The P glycoprotein's pharmacological inhibitors with a potential risk of use in patients with SARS-CoV-2 during hospitalization are amiodarone, clarithromycin, diltiazem, ketoconazole, lansoprazole, omeprazole, and other proton pump inhibitors, nifedipine, paroxetine, sertraline, verapamil, and duloxetine.

Drugs that are potent CYP3A4 inhibitors include (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil.

Patients with inflammation, particularly high acute-phase proteins, such as C-reactive protein (CRP), have reduced the CYP3A4 function. Some drugs can also have an induction effect, which

usually results in a decrease in the action of the medicine, are potent inducers: the phenobarbital and phenytoin [44].

The significant side effects related to the use of colchicine were associated with prolonged use, pre-existing pathological conditions, and interaction with the drugs mentioned before. All patient needs to be monitored to avoid these situations: bone marrow suppression [45], Disseminated Intravascular Coagulation [46], rhabdomyolysis [47], and electrolyte disturbances, including hypokalemia and hyponatremia.

4. Therapeutic doses of colchicine

In the AGREE study (Acute Drop Analysis Receiving Colchicine), which looked at high and low doses of colchicine, that is, 8 versus 3 tablets (0.6 mg) in 24 hours in the initial acute outbreaks, there was no significant difference between both groups, related to symptom relief, but the group with high doses had more gastrointestinal effects [48].

The American College of Rheumatology guidelines also recommended colchicine as an appropriate primary treatment option for acute gout attacks, with an initial dose of 1.2 mg, followed by 0.6 mg every 6 hs [49].

Several studies involving osteoarthritis, liver cirrhosis, and pericarditis, among others, have reported the prolonged use of colchicine safely. In one of those studies total of 120 patients (mean age 56.9 ± 18.8 years, 54 males) with a first episode of acute pericarditis (idiopathic, viral, postpericardiotomy syndromes, and connective tissue diseases) received treatment plus colchicine 1.0–2.0 mg for the first day and then 0.5–1.0 mg/d for 3 months (group II). The primary endpoint was the recurrence rate. During the patient follow-up, colchicine significantly reduced the recurrence rate and have was discontinued in 5 cases (8.3%) because of diarrhea. No serious adverse effects were observed [50].

While this article was being revised, was published the GRECCO-19 Randomized Clinical Trial, where a total of 16 tertiary care hospitals in Greece were activated to recruitments patients between April 3 and April 27, 2020. In this study, 105 patients hospitalized with COVID-19 were randomized in a 1:1. The patients who were randomized to the intervention arm received a loading dose of 1,5 mg of colchicine followed by 0,5 mg of colchicine 60 min later if no adverse gastrointestinal effects were observed. The maintenance dosage was 0,5 mg colchicine twice daily until hospital discharge or a maximum of 21 days. In this Trial, the clinical deterioration rate was higher in the control group than the colchicine group. No difference was observed in the primary biochemical endpoint (high sensitivity troponin concentration), but patients in the colchicine arm had a smaller increase in dimerized plasma fragment D [51].

5. Discussion

Since December 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The WHO classified the novel coronavirus as a global public health emergency on January 30th, and already on March 11th, was reclassified as a pandemic.

We currently have 253,390 deaths worldwide, and there is still no effective treatment for severe cases and no immunization therapy. Current management consists of supportive care in the absence of a proven effective treatment, including invasive and noninvasive oxygen support and treatment with antibiotics [52–54]. Also, many patients have received off-label or compassionate-use therapies, including antiretrovirals, antiparasitic agents, antiinflammatory compounds, immunosuppressive agents, and convalescent plasma [21].

Several studies suggested that the cytokine storm (i.e., higher concentrations of granulocyte-colony stimulating factor, interferon gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 α and tumor necrosis factor α) could be associated with the severity of disease [55]. Another study from China reported that increased expression of IL-2 and IL-6 in serum appears to predict the severity and prognosis of patients with COVID-19 [56].

The chloroquine and hydroxychloroquine can reduce the production of various pro-inflammatory cytokines, such as IL-1, IL-6, interferon- α , and tumor necrosis factor, which are involved in the cytokine storm [57]. However, side effects, mainly cardiovascular, have discontinued use in some countries driven by WHO recommendations.

Several randomized controlled trials are investigating the safety and efficacy of the various antiviral and immunosuppressive agents. Many of these drugs have serious adverse effects, especially when administered to critically ill patients, which may have a negative synergistic effect with other drugs in use [54].

In this paper we suggest using the use of colchicine, a class of drugs with widespread availability and optimal tolerability profile, as an add-on treatment for COVID-19 patients, based on their known immunomodulatory properties.

The colchicine has anti-fibrotic effects as a microtubule-destabilizing agent, which can contribute to the reduction of pulmonary fibrosis as well as the formation of viroporins. The colchicine significantly reduces levels of production the inflammatory cytokines (IL-1 β , IL-18, and IL-6) that contribute to thrombotic microangiopathies. We also know that Inflammatory mediators play a crucial role in the pathogenesis of ARDS, and cytokines contribute to ARDS. Additionally, uncontrolled epithelial cell proliferation and impaired tissue remodeling during later stages induce ARDS leading to pulmonary fibrosis [56].

Based on this evidence, the use of colchicine as an immunomodulatory treatment for COVID-19 may deserve consideration due to the intrinsic metabolic effects demonstrated.

6. Conclusion

Different factors are involved in the outcome of patients receiving treatment against COVID19, including the type of supportive care (for example, medications used or variations in ventilatory practices) and hospitalization limits. In addition, the use of immunosuppressive agents to control the cytokines storm isn't available in poorer countries. Colchicine is a medication that acts on inflammasome NLRP3 and can reduce cytokine storm. Furthermore, it has low cost, was extensively tested and well tolerated, less likely to be affected by a shortage in a health crisis like the current COVID-19 pandemic. This hypothesis should justify the consideration of the more phase III clinical trials.

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