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# Colchicine – from Gout to Covid-19

**Ekadana Prayoga Suryadi*, Keith Justine Thiotansen, Reynaldi Hardianto Saputra, Priscilla Angeline, Novia Yolanda**

Faculty of Medicine, Ciputra University, Surabaya

***Email:**
eprayoga01@student.ciputra.ac.id

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**ABSTRACT**

Colchicine is a toxic and carcinogenic alkaloid obtained from the plant extract Colchium autumnale and has been used to treat arthritis (gout) for centuries. The results of clinical trials show that low-dose colchicine is effective for the management of acute gout as well as for long-term maintenance profiling and the use of colchicine is known to reduce the symptoms of inflammatory responses related to COVID-19 and reduce the frequency of other manifestations such as pulmonary infiltrates, headaches and arthralgia. However, so far studies have shown that colchicine is not used as an initial or primary treatment to treat COVID-19 but as a treatment that is "off-label" in response to hyper-inflammation caused by the release of cytokines.

**Keywords**: colchicine, covid-19, gout



## INTRODUCTION

Colchicine is an anti-inflammatory agent that is widely used as a treatment of autoimmune and inflammatory diseases. The mechanism of action of colchicine is to inhibit the formation and polymeration of microtubules, thereby disrupting the mitotic activity of the cell; in addition, in the immune system colchicine inhibits neutrophil chemotaxis, plays a role in the production of superoxide, inhibits NACHY-LRRPYD-containing protein 3 (NALP3) inflammasome, as well as reduces the release of interleukin 1□ (IL-1□). Colchicine is mainly used as a treatment of gout and mediterranean fever.

Coronavirus Disease 2019 is a respiratory system disease caused by Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2); the disease is usually mild, but sometimes severe and life-threatening (Gendelman O, 2020). Since the onset of the COVID-19 pandemic, experts have begun looking for potential prevention and treatment of the disease, but have yet to find a specific vaccine or medicine that can prevent or overcoming the burden of COVID-19 on patients. Colchicine is one of the drugs tested as a therapy from COVID-19; the drug is considered promising because it can inhibit NLRP3 inflamasomes and reduce interleukin activation (Deftereos S, 2020). This article discusses the mechanism of action of colchicine, the effects of colchicine for gout, to its potential effects for COVID-19 based on sources that can be found online.

Due to the nature of coronavirus infection, a large infiltration of inflammatory cells consisting of innate and adaptive immune cells is observed in the lungs of COVID-19 patients. The presence of these innate immune cells are mostly neutrophils that risk injuring the lungs. It is also observed in SARS-CoV infections, where infected lungs produce IL-8 and IL-6, chemoattractants for both cells, neutrophils and T cells. Reports in patients with severe disease have been shown to have increased concentrations of IL-6, IL-10, G-CSF, MCP1, MIP1α, and TNF-α plasma, with IL-6 growing correlated with the severity of the disease or condition (Yuki K, 2020).

## METHODS AND MATERIAL

### Neutrophils

Inhibition of Neutrophil Chemotaxis

Colchicine is concentrated in leukocytes, with the lowest concentration of 0.1nM which inhibits neutrophil chemotaxis and the release of crystal derived chemotactic factor (CCF) glycopeptide from neutrophil lysosomes after the occurrence of phagocytosis of monosodium urate crystals (MSU). Chemotaxis factor S100A8/9 caused by MSU released from neutrophils showed that it could increase recruitment of neutrophils. Gagné et al demonstrate that colchicine inhibits the fragility of MSU-induced cell surfaces in neutrophils and the production of IL-8 (Fordham JN, 1981).

Neutrophil adhesion, mobilization and recruitment

Through depolymerization, colchicine inhibits the adhesion of neutrophils to inflamed tissues. At doses commonly used in prophylaxis, colchicine changes the distribution of E-selectin on the surface of endothelial cells so that the adhesion in neutrophils disappears. At higher doses, colchicine causes decay from neutrophil adhesive molecules (L-selectin) and inhibits neutrophil recruitment. Paschke et al found that colchicine inhibits the deformability and motility of human neutrophils in narrow spaces, which is crucial to the extravasation of neutrophils at the time of inflammation (Guan T, 2013).

Inhibition of Superoxide Production from Netrofil

Colchicine suppresses MSU-induced superoxide production of neutrophils selectively, this effect is mediated by microtubule inhibition. Chia et al proved that colchicine inhibits MSU-induced superoxide production by peritoneal macrophage murinae at doses that are 100 times lower than those needed to inhibit neutrophil infiltration. This suggests that the production of superoxide anions is more sensitive to the containment of colchicine than microtubule formations involved in cell migration. colchicine has also been shown to reduce oxidative stress by decreasing calcium current ($Ca^{2+}$) in neutrophils (Khanna D, 2012).

Inhibition of NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome

MSU and calcium pyrophosphate dihydrate crystals (CPPD) activate nalp3 inflammasome. At high concentrations (5μM), colchicine inhibits inflammasome NALP3, which activates caspase-1 and processes and releases IL-1β and IL-18. The mechanism of colchincine in inhibiting inflammasome NALP3 is still unknown. The emphasis on inflammasome NALP3 activity occurs at much higher doses compared to doses commonly used in therapeutics so this may not be the primary therapeutic action of colchicine responsible in acute arthropathic crystals. However because the concentration of colchicine in neutrophils is 16 times higher than the peak concentration in plasma [19], a low prophylactic dose of colchicine administered continuously may be able to inhibit activation of nalp3 inflammasome.

### Antigen Stimulation

In relatively low concentrations (3μg/ml), colchicine rats showed maturation of dendritic cells, cytokine formation and antigen presentation against CD4+ lymphocytes. Showing the importance of microtubules in cells when processing antigens, the effect of colchicine that stimulates dendritic cells (as an antigen presenter to cells) has been demonstrated in human dendritic cells.

### Anti-Fibrosis And Cardiovascular Protective Effects

Colchicine has an antifibrosis effect. In trials with a mouse model of cyclosporine nephrotoxicity, colchicine inhibited tubulointersitial fibrosis by stimulating B-cell lymphoma 2 (Bcl-2) and suppressing caspase-3 which caused suppression of renal cell apoptosis. In trials with a mouse model of chronic renal disease hypertension, colchinin inhibited fibrosis in the kidneys by inhibiting RhoA signaling and inflammatory cell infiltration (Mizumoto N, 2005).

In trials with a mouse model, colchicine inhibited fibrosis in the liver by inhibiting the activation of hepatic stelata cells and inhibiting cell-induced apoptosis. In addition, Colchicine also inhibits the activity of transforming growth factor (TGF)-β1 and myofibroblast differentiation in Rho / serum response factor (SRF). In patients with familial mediterranean fever (FMF) given colchicine therapy had signs of endothelial dysfunction and lower cardiovascular risk. Colchicine was shown to have a protective synergistic effect with atorvastatin in endothelial function, as well as reduction of C-reactive protein (CRP) and lipoprotein associated phospholipase A2 (Lp-PLA2) (Roberge CJ, 1993).

**Colchicine Therapy In Treating Covid-19 Sufferers**

In response to the increase in transmission and infection of COVID-19, several treatment efforts have been made to examine the efficacy of the treatment in alleviating the symptoms caused by COVID-19 including colchicine. As a result, the use of colchicine is known to reduce the symptoms of inflammatory responses related to COVID-19 and reduce the frequency of other manifestations such as pulmonary infiltrates, headaches and arthralgia. However, so far studies have shown that colchicine is not used as an initial or primary treatment to treat COVID-19 but as a treatment that is "off-label" in response to hyper-inflammation caused by the release of cytokines (Della-Torre E, 2020).

Extreme pro-inflammatory responses or "cytokine storms" are characteristic of severe COVID-19 infection, which can lead to Acute Respiratory Distress Syndrome (ARDS) and multiple organ failures, believed to be caused by alveolar epithelial injury and capillary endothelium injury with immune system abnormalities. the treatment of COVID-19 is that the toxicity of colchicine, as opposed to the treatment of COVID-19, risks causing ARDS due to the active infection itself and the dissemination of intravascular coagulation (DIC) or coagulopathy. However the properties of colchicine itself can be used to reduce the risk of ARDS as well when used carefully and appropriately to reduce pressure on emergency departments, even hospitalizations.

Although several studies are ongoing, as of March 30, 2020, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the European Medicines Agency and the World Health Organization (WHO) have not discussed or recommended colchicine as a drug. therapeutic treatment for patients with COVID-19, and further evaluation and study are still needed to fully understand the role of colchicine in treating covid-19 patients going forward.

**Mechanism Of Action**

Tubulin Disruption and the Anti-Mitosis Effect of Colchicine

From many studies and trials that have been carried out it is known that the mechanism of therapeutic action possessed by colchicine is its ability to bind to tubulin, which inhibits the formation and polymerization of microtubules. Microtubules are important components of the cytoskeleton, which are formed from the heterodimer αβ-tubulin and function against several cellular activities that include the maintenance of cell shape, secretion of cytokines and chemokines, cell migration, regulation of ion canals and cell division. Colchicine binds with tubulin and forms tubulin-colchicine of a non-reversible nature, which eventually binds at the end

In low consensation colchicine will inhibit the growth of microtubules and at high concentrations cause depolymerization of microtubules. In high doses can cause severe toxicity of the tissues, which limits their use in cancer therapy (Abanonu GB, 2012). Other effects of colchicine on malignancy include inhibition from cancer cell migration and metastatic potential (Asako H, 1992). Cell blebbing through the Rho/Rho kinase (ROCK)/myosin light chain kinase (MLCK) pathway (Bhattacharyya B, 2008). Angiogenesis inhibitor (Borstad GC, 2004). Adenosine triphosphate (ATP) current restriction towards mitochondria (Bozkurt D, 2008). And caspases and cytochrome-c discharges that cause apoptosis. Colchicine also has an anti-inflammatory effect, especially against disturbances in the microtubules and the cellular current function of leukocytes.

Mechanism of Action of Colchicine On The Immune System

The main mechanisms of colchicine against the immune system are inhibition of neutrophil chemotaxis, adhesion and mobilization, production of superoxide and inhibition of inflammasome NACHT-LRRPYD-containing protein 3 (NALP3), as well as the processing and release of interleukin 1β (IL-1β) (Charpentier MS, 2014).

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## RESULT

### Colchicine For Gout

Colchicine is very often used in tackling acute gout attacks, from the AGREE (Acute Gout Flare Receiving Colchicine Analysis) trial which tested high-dose colchicine (8 tablets) and low doses (3 tablets) with the caption 1 tablet having a dose of 0.6 mg and placebo in patients with the first 24 hours of acute gout attacks , showing the superiority of colchicine compared to placebo in 185 pasien yang diacak dari colchicine dosis tinggi hingga rendah dan placebo dengan tingkat respon 32.7% (dosis tinggi), 37.6% (dosis rendah), dan 15.5% (placebo) (Ryckman C, 2003). High dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group. The general consensus for the treatment of acute gout is to use low doses of colchicine. By looking at the side effects that include kidney, liver, and gastrointestinal disorders, dosage settings should be high dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects. In addition to avoiding the use of colchicine with interacting drugs, dose reduction should be considered in patients with renal or hepatic impairment, as well as in the elderly. Some recommendations suggest a dose reduction of up to 50% in patients with CrCl 50 ml/min. (Shu JC, 2009). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group. The general consensus for the treatment of acute gout is to use low doses of colchicine. By looking at the side effects that include kidney, liver, and gastrointestinal disorders, dosage settings should be high dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group. The general consensus for the treatment of acute gout is to use low doses of colchicine. By looking at the side effects that include kidney, liver, and gastrointestinal disorders, dosage settings should be high dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group. The general consensus for the treatment of acute gout is to use low doses of colchicine. By looking at the side effects that include kidney, liver, and gastrointestinal disorders, dosage settings should be 185 patients were randomized from high to low doses of colchicine and placebo with response rates of 32.7% (high dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group. The general consensus for the treatment of acute gout is to use low doses of colchicine. By looking at the side effects that include kidney, liver, and gastrointestinal disorders, dosage settings should be observed. EULAR (The European League against Rheumatism) 2011 consensus guidelines recommend low-dose colchicine, with doses up to 3 doses with a dose of 0.5mg in the first 24 hours of treatment of gout (Taskiran EZ, 2012). ACR guidelines also recommend colchicine as the primary treatment for acute gout attacks, with an initial dose of 1.2 mg followed by a dose of 0.6 mg. High dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group. The general consensus for the treatment of acute gout is to use low doses of colchicine. By looking at the side effects that include kidney, liver, and gastrointestinal disorders, dosage settings should be. In addition to avoiding the use of colchicine with interacting drugs, dose reduction should be considered in patients with renal or hepatic impairment, as well as in the elderly. Some recommendations suggest a dose reduction of up to 50% in patients with CrCl 50 ml/min.

## CONCLUSION

Coronavirus Disease 2019 is a respiratory system disease caused by Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2); the disease is usually mild, however sometimes severe and life-threatening. Colchicine is one of the drugs tested as a therapy from COVID-19; This drug is considered promising because it can inhibit NLRP3 inflamasomes and reduce the activation of interleukin. patients randomized from high to low doses of colchicine and placebo with response rates of 32.7% (high dose), 37.6% (low dose), and 15.5% (placebo). There were no significant differences in the high-dose and low-dose groups, only that the high-dose group had more gastrointestinal side effects than the low-dose group.

## DISCUSSION

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### Toxicity And Metabolism Of Colchicine

Colchicine has a narrow therapeutic window. When administered on a daily basis to FMF patients, the most frequent reactions (up to 20%) are abdominal pain, diarrhea, nausea, and vomiting. These side effects are usually mild, temporary, and reversible by reducing the dosage. Prescribed acutely for gout at a dose of 1.8mg within 2 hours, the most frequent reactions are diarrhea (23%) and pharyngolaryngeal pain (3%). At therapeutic doses, blood dysrasia was found that included myelosupression, leukopenia, granulocytopenia, thrombocytopenia, pancytpenia, and aplastic anemia (Sandbo N, 2013). Colchicine is eliminated primaryly through hepatobiliary excretion. Renal excretion contributes by 10-20% in patients with normal renal function. Some types of oobats increase the toxicity potential of colchicine through modulating the activity of P-gp and CYP3A4. Colchicine is eliminated primaryly through hepatobiliary excretion. Renal excretion contributes by 10-20% in patients with normal renal function. Some types of oobats increase the toxicity potential of colchicine through modulating the activity of P-gp and CYP3A4. Cases such as myopathy and/or rhabdomyolysis were reported in patients taking colchicine with statins, fenofibrate/gemfibrozil, cyclosporine, or digoxin. Toxicity was also reported in patients who consumed grape juice daily. Once the ingestion of colchicine is stopped, the symptoms usually disappear within 1 week to several months. Life-threatening interactions occurred in patients administered colchicine with P-GP inhibitors (cycosporine, ranolazine) and powerful CYP3A4 inhibitors (clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, and some protease inhibitors).

In addition to avoiding the use of colchicine with interacting drugs, dose reduction should be considered in patients with renal or hepatic impairment, as well as in the elderly. Some recommendations suggest a dose reduction of up to 50% in patients with CrCl 50 ml/min. In addition to avoiding the use of colchicine with interacting drugs, dose reduction should be considered in patients with renal or hepatic impairment, as well as in the elderly. Some recommendations suggest a dose reduction of up to 50% in patients with CrCl 50 ml/min.

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