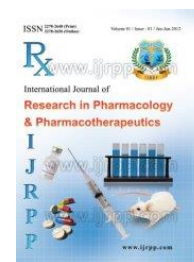




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Review Study

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### Revisiting anti-inflammatory potential of colchicine and repurposing use of colchicine in Covid-19: A comprehensive review

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#### ABSTRACT

Colchicine is a known anti-inflammatory and antiproliferative drug obtained from plant known as *Colchicum autumnale*. In the past it has been used as an anti-inflammatory drug in the gout and mediterranean fever and in several off label conditions. Despite concerns about its gastro-intestinal tolerability, drug interactions and narrow therapeutic window, colchicine has shown promise in many cardiovascular diseases including chronic pericarditis and ischaemic heart disease. Present review has been done with an objective to explore therapeutic and pleotropic anti-inflammatory effects of colchicine in various inflammatory clinical conditions including Covid-19 (SARS-CoV-2). Literature search has been carried out by all researchers using databases PubMed/MEDLINE, Google Scholar, EMBASE, SCOPUS and Cochrane (central) review. In the era of Covid-19, researchers across the globe are repurposing and exploring the role of colchicine in Covid-19 induced cytokine storm and inflammation. Using formulations of colchicine through targeted drug delivery approach may help in greater safety and acceptability of colchicine for various inflammatory conditions.

**Keywords:** Colchicine, anti-inflammatory, anti-proliferative, Covid-19

#### INTRODUCTION

Colchicine, is an alkaloid drug, obtained from a plant known as *Colchicum autumnale* approved by FDA in 1961 for the treatment of acute gout and familial Mediterranean fever (FMF) as well as for prophylaxis of gout.<sup>1,2</sup> (Fig 1) The 'Off-label' uses of colchicines are in several conditions like acute gout, sarcoid, psoriatic arthritis, behcet's disease, pericarditis, amyloidosis, scleroderma, primary biliary cirrhosis, hepatic cirrhosis, dermatitis

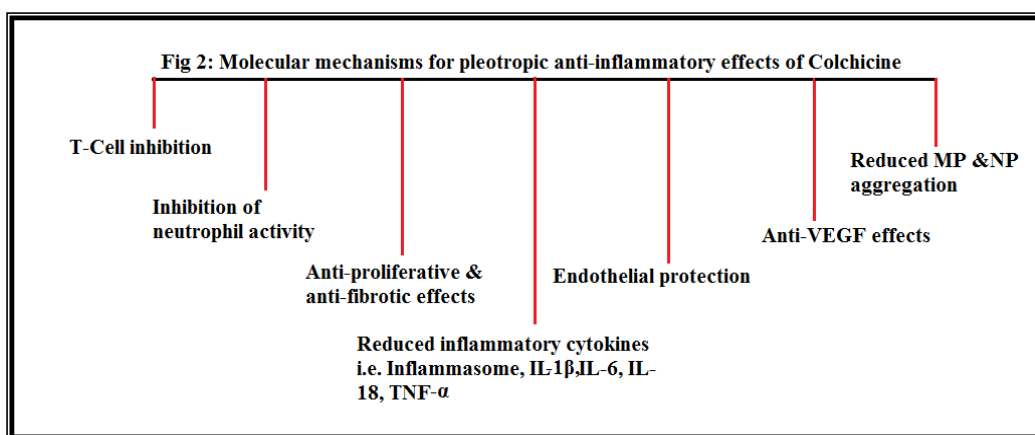
herpetiformis, paget's disease of bone, chronic immune thrombocytopenia and idiopathic thrombocytopenic purpura, idiopathic pulmonary fibrosis and prevention of post pericardial syndrome. Its beneficial role in these wide varieties of conditions has been ascribed to its anti-inflammatory and antiproliferative actions. (Fig 2) Present review has been done with an objective to explore therapeutic and pleotropic anti-inflammatory effects of colchicine in various inflammatory clinical conditions including Covid-19 (SARS-CoV-2).



**Fig 1: Colchicine flowers**

Colchicine exhibits its anti-inflammatory and antiproliferative actions through various mechanisms. Colchicine inhibits the assembly of microtubules by forming a tubulin-colchicine complex. As a result, release of inflammatory mediators and movement of intercellular granules is interfered with.<sup>3</sup> It gets accumulated in the leucocytes and diminishes their motility. It affects the adhesion of neutrophils to vascular endothelium and cytokines synthesis such as interleukin-1 beta.<sup>4</sup> This mechanism play a vital role in the interruption of inflammatory cell activation. Colchicine gets accumulated in the leucocytes at a concentration higher than plasma levels, resulting in suppression of these cells at clinically used doses.<sup>5</sup> Colchicine is also found to suppress activation of the Nod-Like Receptor Protein 3 (NLRP3) inflammasome, resulting in suppression of caspase-1 activation and release of IL-1 $\beta$  and IL-18.<sup>6</sup> It is useful in treating neutrophils and monocytes/ macrophages associated diseases as NLRP3 inflammasome are found in myeloid lineage cells.<sup>7</sup>

Colchicine is generally a tolerated medicine with common adverse effects related to gastrointestinal tract, which includes nausea, vomiting and abdominal pain. Other dose related adverse effects include hair loss, weakness, and nerve irritation.<sup>8</sup> It is metabolised in the liver by cytochrome p450 (CYP 450) enzymes and eliminated from the body by P-glycoprotein transporter or through glomerular filtrations in the kidneys. Therefore dose adjustment for colchicine is required in patients with deranged liver and kidney function tests.<sup>9</sup> Cytochromal enzyme inhibitors e.g. azithromycin should be avoided with colchicines due to risk of toxicity of colchicines by increased plasma levels of later.<sup>9</sup> Several studies have reported drug interaction between colchicine and statins, mainly with Atorvastatin and Simvastatin, which are metabolised by CYP3A4. Both of these drugs can individually cause myopathy and thereby increases the risk when given together. In case symptoms of colchicine toxicity seen, it should be stopped immediately. The symptoms resolve within 1 week to several months.<sup>10</sup>



IL- Interleukin, TNF- Tumor necrosis factor, VEGF- Vascular endothelial growth factor, MP- Monocyte platelet, NP-Neutrophil platelet

**Fig 2: Molecular mechanisms for pleotropic anti-inflammatory effects of Colchicine**

**Role of Colchicine in Cardiovascular diseases**

Inflammation plays a central role in the development and progression of coronary disease.<sup>11,12</sup> Therefore, anti-inflammatory drug interventions may reduce the risk of cardiovascular events.<sup>13</sup> Patients of

chronic coronary disease remain at high risk for acute cardiovascular events despite attempts of reduction of risk factors including life style modification.<sup>14</sup> Colchicine being an antiinflammatory drug has been found to lower the risk of cardiovascular events in patients of chronic coronary disease at a dose of 0.5mg

given daily.<sup>15</sup> It also significantly lowers the risk of ischemic cardiovascular events in patients with a recent myocardial infarction.<sup>16</sup> It is found to target mechanisms which play a role in the pathogenesis of coronary artery disease like MI. Colchicine may prevent left ventricular remodelling and improve cardiac survival. Colchicine along with antiplatelet therapy with Aspirin or Statin in patient with coronary artery disease (CAD) reduces the risk of acute coronary syndrome and cardiac arrest as compared to CAD patients who were not given colchicine along with medical therapy.<sup>17,18</sup> Retrospective studies in gout patients, who are at risk of cardiovascular disease, have also demonstrated that colchicine reduced the prevalence of MI as compared to the gout patients who did not receive colchicines.<sup>19,20</sup>

One of the study has shown that colchicine cause reduction in the clot size or its propagation, that occur at the inflammatory site.<sup>21</sup> However, a double-blind placebo-controlled multicenter trial have shown that oral administration of colchicine 2-mg loading dose followed by 0.5 mg twice a day, at the time of reperfusion and for 5 days did not reduce infarct size and left ventricular remodelling even at 3months of follow up.<sup>22</sup>

### Colchicine in anti-cancer therapy

Colchicine is not recommended these days for treatment of cancer due to its systemic toxicity. Although, clinically acceptable dose of colchicine has shown to have anti-cancer potential in hepatocellular and prostate cancers and can be used as palliative treatment. Colchicine when used in dose of 6 ng/mL on both hepatocellular carcinoma demonstrated equivalent efficacy as seen with use of 1 µg/mL epirubicin.<sup>23,24,25</sup> Several semisynthetic and synthetic analogues of Colchicine are being explored worldwide to be used as potential anticancer drugs with an objective to increase safety by using novel targeted drug delivery approaches for enhancing its future acceptability among patients.<sup>26</sup>

### Colchicine in Dermatological conditions

Colchicine is not recommended as first line therapy for cutaneous/dermatological inflammatory conditions. A systematic review has revealed that colchicine has been found useful in primary localised cutaneous amyloidosis, cutaneous vasculitis, psoriasis, chronic urticaria, epidermolysis bullous acquisita, palmoplantar pustulosis, eccrine hidradenitis, acne vulgaris, behçet's disease, pigmented purpuric dermatoses, cutaneous amyloidosis, cutaneous sarcoidosis, hereditary angioedema, pemphigus and stomatitis.<sup>27</sup>

### Other uses of colchicine

Recently, colchicine has been found to be effective in cases of life-threatening post-transplant capillary leak syndrome owing to anti-inflammatory and immunomodulatory function. These patients needed mechanical ventilation and hemodialysis for several weeks prior to receiving colchicine. Addition of colchicine helped in restoring normal respiratory function and diuresis over 48 hrs in these patients.<sup>28</sup>

### Considerations in Children

Colchicine is most commonly used in children to treat periodic fever syndromes and auto-inflammatory conditions. Although colchicine is generally considered safe and well tolerated in children, there are no data on the use of the drug to treat paediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).

### Recent interest in the use of colchicine in Covid-19

Coronavirus disease 2019 (COVID-19), is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Its clinical manifestations varies from asymptomatic carriers, which account for more than 80% cases to symptomatic patients who develop mild, moderate or severe pneumonia symptoms followed by respiratory failure.<sup>29</sup> The clinical condition in Covid-19 gets complicated in patients with co-morbidity leading to underlying lung inflammation following cytokine storm and thrombogenesis.<sup>30,31</sup>

There is an upcoming interest to explore the role of colchicine in Covid-19, owing to its anti-inflammatory and anti-proliferative potential. Colchicine available as oral formulation, stands different from all other drugs approved for Covid-19 including tocilizumab, molnupiravir, remdesivir etc, due to less affinity for single target, acting through different mechanisms and exhibiting pleotropic effects. Colchicine is an inexpensive immuno-modulator drug, but not immunosuppressant drug, when used in cytokine storm in Covid-19 patients, is not known to increase risk of acquiring opportunistic infections.<sup>4,32</sup> Studies have shown that, colchicine, when administered early in the course of COVID-19, has the potential to prevent inflammation-associated manifestations of the disease. A randomised study, done in hospitalised covid-19 patients, who received colchicine have shown reduction in deterioration of their clinical status.<sup>33</sup> Another retrospective cohort study have stated that colchicine reduced the mortality and enhanced the recovery in COVID-19 patients by suppressing cytokine storm and staggering fibrotic lung changes.<sup>34</sup> There are two small case series which

have reported the clinical benefit of colchicine in outpatients of COVID-19<sup>35,36</sup> whereas a double blind study performed on outpatients of COVID-19, who received colchicines 0.5mg, twice daily for 3 days followed by once daily for 27days or placebo have shown no statistically significant differences in the death or hospitalization and the need for mechanical ventilation by Day 30.<sup>37</sup> Another study in hospitalized patients with COVID-19 who received colchicine and were also on corticosteroids, have shown no statistically significant differences in the discharge time, receiving mechanical ventilation or death.<sup>38</sup> Hence there is a need to conduct larger randomized controlled trials to test the efficacy of colchicine in COVID-19 patients. Study by Tardif et al has revealed that colchicine being safe, available orally and cheap medicine, can be beneficial in co-morbid patients showing positive PCR for Covid-19, who are non-co-operative for receiving parental drug therapies.<sup>37</sup>

## CONCLUSION

Colchicine, available as oral formulation, is economical, affordable and has good patient compliance. In addition to its well-established roles in treating gout and FMF, colchicine has demonstrated benefit in a variety of cardiac diseases, including pericarditis and coronary artery disease. The established potential benefits due to broad anti-inflammatory potential are compelling thoughts for repurposing its use in emerging inflammatory conditions including Covid-19. Several synthetic and semisynthetic analogues of Colchicine are continuously being explored for novel indication using targeted drug delivery approach, which will increase its acceptability in near future. Given its relatively good safety and tolerability profile when used in low dose carefully and appropriately, colchicine will continue to be a part of the anti-inflammatory regimens for years to come. More safety and efficacy studies are required to establish its role in Covid-19.

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