



# A Comprehensive Review of Colchicine: An Ancient Drug with Many Therapeutic Potentials

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## ABSTRACT

In this study, we aimed to review the literature and formulate a comprehensive understanding of colchicine and its therapeutic potential. Colchicine is one of the oldest treatments which are still used today. Colchicine is an alkaloid agent that has anti-inflammatory and pain-relieving effects. It has been used to treat inflammatory diseases such as gout, familial Mediterranean fever (FMF), and Behcet's disease. Colchicine's ability to reduce inflammation is linked to its interaction with tubulin, a cytoskeletal structure. Colchicine inhibits neutrophil adhesion, migration, and chemotaxis. Tyrosine phosphorylation, which is crucial for neutrophil activation, is specifically inhibited by colchicine. Additionally, colchicine inhibits neutrophil deformability, which influences neutrophil extravasation. Colchicine inhibits the production of superoxide and the release of interleukin 1 $\beta$  and IL-6. Colchicine decreases the production of inflammasomes that stimulate caspase-1 activation and release of interleukins. Colchicine has gained attention during the COVID-19 pandemic to treat severe COVID-19 cases and to decrease mortality. Colchicine is considered a safe drug with high availability and affordability. Colchicine metabolism is affected by cytochrome P450 (CYP3A4) and P glycoprotein inhibitors, and renal and hepatic function impairment. The most documented adverse effects of colchicine are gastrointestinal symptoms e.g., diarrhea, vomiting, and nausea.

**Key Words:** Colchicine, Mechanism of action, Indications, Review, Ain Shams University

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## INTRODUCTION

Colchicine is considered one of the oldest treatments which are still used today. In 1550 BC, colchicine was found prescribed in an Egyptian papyrus. It was also used by ancient Greek, Byzantine, and Arabian physicians [1]. In 1952, X-ray crystallography was a cornerstone tool in the visualization of the structure of colchicine and the synthesized form was fully established in 1959 [2]. Colchicine has anti-inflammatory and pain-relieving effects. It is an alkaloid agent that was derived from a plant called autumn crocus or *Colchicum autumnal*. It was first synthesized in the nineteenth century. Since then,

colchicine has been used to treat joint pain and to alleviate inflammatory diseases such as gout, familial Mediterranean fever (FMF), Behcet's disease, and pericarditis [1]. The anti-inflammatory role of colchicine is related to its interaction with a cytoskeletal structure called tubulin. In addition, colchicine has gained attention during the Coronavirus disease 2019 (COVID-19) pandemic. It represents a potential anti-inflammatory agent to treat severe COVID-19 cases and to decrease mortality among those patients [3] Colchicine is considered a safe drug with high availability and affordability [4].

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This study aimed to review the literature and provide a comprehensive understanding of colchicine with a highlighting of its different therapeutic roles.

## MATERIALS AND METHODS

We utilized the following databases to retrieve the medical literature related to Colchicine: PubMed, ScienceDirect, and Google Scholar. The search terms, used both separately and in combination, included: "Colchicine," "Mechanism of action," "Indications," and "Properties." Only articles in English were included.

### Discussion

#### Structure and physical properties

Colchicine structure is derived from the precursors of the amino acids phenylalanine and tyrosine and is composed of an alkaloid, tricyclic, lipid-soluble formula (C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>). The tricyclic structure of colchicine is composed of ring A with a tri methoxyl group, a seven-membered ring named ring B, and a tropologic ring under the name ring C [5].

The average weight of a colchicine molecule is 399.437 g/mol and its melting point ranges between 142 & 150°C. Colchicine is considered a sensitive compound to light; therefore, it should be kept in dark containers. When it is exposed to light, it darkens and changes through photoisomerization into isomer molecules that are called lumicolchicine. This transformation makes colchicine lose its effectiveness in binding to tubulin and it becomes an inactive drug [6].

#### Pharmacokinetics

The absorption of Colchicine occurs mainly in jejunum and ileum and its bioavailability ranges between 25% and 50%. It remains detected in leukocytes for up to 10 days after oral intake. The intravenous form of colchicine has a shorter half-life, and it is not used now due to its toxicity [7]. Colchicine is mainly eliminated through P-glycoprotein that is available in hepatocytes, enterocytes, renal tubules, monocytes, and the blood-brain barrier. A significant amount of orally administered colchicine metabolism occurs via hepatic cytochrome P450 (CYP3A4) or exerted by glomerular filtration. Therefore, these mechanisms make colchicine susceptible to drug interaction with different medications that inhibit CYP3A4 such as clarithromycin, calcium channel blockers, many HIV drugs, antifungals, and P-glycoprotein inhibitors including ranolazine and cyclosporin, and such interaction may result in accumulation of colchicine and potential toxicity [8].

#### Mechanism of action

#### Effect of colchicine on tubulin

Colchicine has been known to exert its anti-inflammatory effect by binding to the tubulins and inhibiting the polymerization of microtubules which represent a key component of the cytoskeleton. Tubulin heterodimers make up microtubules, which are crucial for a variety of cellular processes such as intracellular trafficking, cell shape, migration, and division. Colchicine and tubulin combine to generate a complex that attaches to microtubules and stops them from elongating. Colchicine thereby prevents mitotic division during metaphase [9].

#### Effect of colchicine on the immune system

Colchicine significantly declines neutrophil chemotaxis, migration, and adhesion through microtubule depolymerization. Also, colchicine dampens neutrophil adhesion by altering E-selectin molecules on the endothelial surface. At a higher concentration of colchicine, it promotes the shedding of L-selectin adhesion molecules on neutrophils and prevents their recruitment [10].

Recently, colchicine selectively inhibits tyrosine phosphorylation which has a significant role in neutrophil activation. Also, colchicine affects neutrophil extravasation by inhibiting the deformability of neutrophils. Colchicine decreases oxidative stress by inhibiting the influx of calcium into neutrophils [11].

In addition, colchicine inhibits the production of superoxide and the release of interleukin 1 $\beta$  and IL-6 which play a role in the inflammatory response. Colchicine prevents the inflammatory cascade by decreasing the production of inflammasomes that stimulate caspase-1 activation and release of interleukins such as interleukin 1 $\beta$  and interleukin IL18 [12, 13].

#### Anti-fibrotic effect and cardiovascular protection

Colchicine has an anti-fibrotic effect by inhibiting the caspase 3 pathways and subsequently decreasing cell apoptosis. Also, colchicine dampens the differentiation of myofibroblast and the release of anti-fibrotic mediators including anti-transforming growth factor (TGF- $\beta$ 1) [14]. The cardiovascular protective role of colchicine occurs by declining the expression of vascular endothelial growth factor (VEGF), tumor necrosis- $\alpha$  (TNF- $\alpha$ ), and C-reactive protein (CRP). Moreover, colchicine inhibits the proliferation of vascular smooth muscles and intimal hyperplasia. Colchicine has a synergistic effect with atorvastatin in cardiovascular protection and increases nitric oxide (NO) production. Therefore, colchicine results in lower levels of the markers of cardiovascular risk including mean platelet volume and  $\beta$ -thromboglobulin [14].

### *Anti-viral effect of colchicine*

Tubulin molecules affect viral replication and intracellular trafficking in viruses that contain a microtubule network. Colchicine inhibits the microtubule polymerization and assembly and subsequently decreases the viral replication in flaviviruses such as Zika and dengue viruses [15].

Some RNA viruses including coronaviruses use the host cell membrane for replication and transcription. This is done by using microtubule-based transport and forming the infected viral particles. The cellular infection by coronaviruses is mediated by the interaction between the spike protein and cytoskeletal structures such as tubulin. Also, microtubules participate in the transport of spike proteins on the virions. Therefore, colchicine plays a significant role in preventing the viral entry and replication of coronaviruses [16].

Coronaviruses significantly activate the production of various inflammatory mediators such as interleukin 1 $\beta$ , interleukin 6, and tumor necrosis- $\alpha$ . Then, these mediators stimulate the NLRP3 inflammasome which results in the inflammatory cascade. Inhibition of such inflammatory mediators by colchicine decreases the inflammatory response and systemic affection by coronaviruses [17]. In recent meta-analyses, colchicine was found to decrease mortality among COVID-19 patients [3, 18]. On the other hand; two studies did not show a significant effect on mortality among COVID-19 patients [19, 20]. Lopes *et al.* documented that colchicine resulted in a significant decrease in the need for oxygen in patients with COVID-19 [21]. These effects justified the repurposing of colchicine and considering it as a therapeutic agent for COVID-19.

### *Indications*

Colchicine is well known as a Food and Drug Administration (FDA)-approved prophylactic and curative agent for gout. Also, it is approved for the treatment of familial Mediterranean fever [22].

Recently, colchicine has been used in the management of the following diseases [23]:

- Osteoarthritis
- Behcet's disease
- Prevention of the post-pericardial syndrome
- Pericarditis
- Pseudogout
- Idiopathic pulmonary fibrosis
- Hepatic cirrhosis
- Paget's disease
- Primary biliary cirrhosis
- Dermatitis herpetiformis

### *Administration*

Colchicine is mainly administered through the oral route. It is available in many forms including tablets, capsules, oral solutions, and gel. The concentration of both tablet and capsule is 0.6 mg while the oral solution is available at a concentration of 0.6mg/5mL. There is a topical form of Colchicine, but it is rarely used [24].

During the acute gout flare, the recommended dose of colchicine is 1.2 mg at the first sign then 0.6 mg 1 hour later. Prophylaxis is continued 12 hours after the acute flare. The prophylactic dose of colchicine for gout is 0.6 mg once or twice daily in adults and children older than 16 years old; not to exceed 1.2 mg daily [24].

The recommended dose of colchicine for Familial Mediterranean fever is 1.2 mg to 2.4 mg for adults and children over 12 years old; the daily dose can be given as a single dose or divided into two doses. The maximum daily dose is 2.4 mg/day [25].

### *Adverse effects*

The most documented adverse effects of colchicine are gastrointestinal symptoms such as diarrhea, vomiting, and nausea. The following adverse effects are less commonly reported, and they are reversible on discontinuation of colchicine [26]:

- Sensorimotor neuropathy.
- Alopecia.
- Maculopapular rash.
- Purpura.
- Lactose intolerance.
- Leukopenia.
- Granulocytopenia.
- Thrombocytopenia.
- Pancytopenia.
- Aplastic anemia.
- Elevated liver enzymes.
- Myopathy.
- Muscle weakness and pain.
- Rhabdomyolysis.
- Azoospermia and oligospermia.

### *Contraindications*

Colchicine metabolism occurs mainly in the liver and other tissues. This metabolism requires P glycoprotein transport and cytochrome P450 (CYP3A4). Colchicine is excreted either unchanged or metabolized in urine. Therefore, colchicine metabolism is markedly affected by CYP3A4 and P glycoprotein inhibitors and renal and hepatic function impairment. The CYP3A4 inhibitors include ketoconazole, itraconazole, fluconazole, atazanavir, indinavir, clarithromycin, erythromycin, and grapefruit juice while P glycoprotein inhibitors involve cyclosporine, and ranolazine [27].

These agents lead to a decrease in the metabolism of colchicine and subsequently its accumulation and serious adverse events up to death. For this reason, dose adjustment of colchicine or alternative agents is recommended in patients with hepatic or renal impairment. Also, the combination of colchicine and CYP3A4P or glycoprotein inhibitor is contraindicated in case of hepatic or renal impairment [27].

#### *Monitoring and precautions*

There is no available test to measure the serum concentration of colchicine. Thus, a complete blood count (CBC) and hepatic and renal function tests are recommended in patients taking colchicine and either CYP3A4 or P-glycoprotein inhibitors. These tests also should be done for patients with hepatic or renal impairment and receiving colchicine. The patients on regular dialysis need a dose reduction as the dialysis does not clear colchicine [24].

Colchicine is known to cause bone marrow suppression even in therapeutic doses and it worsens the already existing blood dyscrasias. Thus, colchicine is used with caution in patients with bone marrow suppression especially if it is utilized for a prolonged period [28].

It has been documented that chronic use of colchicine may result in neuromuscular side effects and rhabdomyolysis. The risk of myopathy is increased with certain drugs including Atorvastatin, Pravastatin, Fluvastatin, Simvastatin, Fenofibrate, and Gemfibrozil [29].

Elderly patients are highly susceptible to developing neuromuscular adverse effects and rhabdomyolysis even without hepatic or renal impairments. Therefore, dose adjustment of colchicine should be done in this age group [29, 30].

Colchicine is classified as category C for pregnant patients. It can be used only if the maternal benefits outweigh the possible fetal risks. In addition, colchicine is found to be excreted in breast milk. However, no adverse reactions in breastfed infants have been reported. This is why The American Academy of Pediatrics considers that colchicine can be used for breastfeeding patients [31].

#### *Toxicity*

The exact dose of colchicine that causes toxicity is undetermined. However, the mortality caused by colchicine reaches 100% in patients who ingest more than 0.8 mg/kg. The symptoms of toxicity start within 24 hours and mainly include gastrointestinal manifestations and marked fluid loss. Within 24 to 72 hours, life-threatening conditions occur and lead to multi-organ failure. Death occurs as a result of cardiovascular collapse, and respiratory failure.

The treatment of colchicine toxicity should be initiated with gastric lavage and anti-shock measures. There is no

specific antidote and dialysis does not eliminate colchicine. Therefore, the treatment is based on symptomatic and supportive measures [32].

## CONCLUSION

Colchicine is an old alkaloid drug that has anti-inflammatory and pain-relieving effects. It is used to treat inflammatory diseases such as gout, familial Mediterranean fever (FMF), and Behcet's disease. Additionally, Colchicine has gained attention during the COVID-19 pandemic to treat severe COVID-19 cases and to decrease mortality. Colchicine interacts with tubulin, a cytoskeletal structure and inhibits neutrophil adhesion, migration, and chemotaxis. Also, it inhibits Tyrosine phosphorylation, which is crucial for neutrophil activation. Colchicine inhibits the release of interleukins such as interleukin 1 $\beta$  and IL-6. Colchicine decreases the production of inflammasomes that stimulate caspase-1 activation and the production of superoxide. Colchicine is considered a safe drug with high availability and affordability. Colchicine metabolism is affected by cytochrome P450 (CYP3A4) and P glycoprotein inhibitors, and renal and hepatic function impairment. The most documented adverse effects of colchicine are gastrointestinal symptoms e.g., diarrhea, vomiting, and nausea.

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