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COLCHICINE: THE HERO CHEMICAL IN THERAPEUTICS

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ABSTRACT

Colchicine is a phytochemical extracted commercially from two plants of the Colchicaceae family, **Gloriosa superba** (flame lily) and **Colchicum autumnale** (autumn crocus). One of the seven upavishas (semi-poisonous drugs) in Indian medicine, colchicine is claimed to treat a number of illnesses but can be lethal if administered improperly. Colchicine dosages greater than 10 mg in humans are always fatal within three days. Due to colchicine's potent anti-inflammatory properties, it can cure many cardiovascular conditions, including coronary artery disease, atherosclerosis, recurring pericarditis, vascular restenosis, heart failure and myocardial infarction. Colchicine has lately demonstrated therapeutic effectiveness in reducing COVID-19 cardiovascular complications. The research on colchicine's anti-inflammatory mechanisms is gaining popularity. The ability of colchicine to inhibit microtubule formation is mainly responsible for its anti-inflammatory effects. Colchicine blocks the following cellular processes: platelet stimulation, macrophage chemotaxis, migration and adhesion, smooth muscle cell growth and migration, and endothelial dysfunction and inflammation. Colchicine suppresses NF-κB signaling, the release of proinflammatory cytokines, and the activation of the NLRP3 inflammasome at the molecular level. In the present review, we are covering the reported mechanism of colchicine used as a drug in various diseases.

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INTRODUCTION

Colchicine is a phytochemical extracted commercially from two plants of the Colchicaceae family, Gloriosa superba (flame lily) and Colchicum autumnale (autumn crocus). The colchicine-type alkaloids are distinctive to the Colchicaceae family and have significant medicinal utility. Autumn crocus (C. autumnale) contains 0.1-0.6% colchicine**.** G. superba roots and seeds have yielded several colchicine-related alkaloids. Colchicine and its derivatives,essential alkaloid for pharmaceutical use, is present in high concentrations in both the plant's tubers and seeds, 2–5 times lower in the latter. Up to 0.9% of colchicine and 0.8% of colchicoside can come from a single plant of G. superba. Its seeds and tubers are highly poisonous due to high levels of colchicine. When compared to seeds, tubers have a reduced colchicine content. Colchicine has been used to cure gouty arthritis since time immemorial. Colchicine is a substitute for those patients unable to handle nonsteroidal anti-inflammatory drugs (NSAIDs) used in gout treatment. Colchicines generally block many pro-inflammatory pathways while promoting higher amounts of anti-inflammatory mediators. Colchicine is used to cure familial Mediterranean fever and Behçet's disease and to avoid heart conditions like pericarditis. (Brvar, Ploj andKozelj, 2004), (Kumar, Sharma and Mondhe, 2017), (Mishra and Sharma, 2020), (Sharma and Mishra, 2022).

Colchicine as a drug for the treatment of cancer: Cancer may develop almost everywhere in the human body, which contains billions of cells. Normally, human cells grow and multiply to produce new cells as the body requires them. When cells become damaged or senescent, they die, and new cells take their place. Sometimes this orderly process is disturbed, and damaged or abnormal cells multiply and grow. These cells may make lumps of tissue called tumors. Tumors can be non-cancerous (benign) or cancerous.

Effect on cell viability: Colchicine's in vitro cytotoxic effect on different cell lines was noted in a dose-dependent way. Purified colchicine demonstrated the lowest cytotoxicity at low doses and a plateau-shaped dose-response curve at higher concentrations, suggesting that the cells become resistant to colchicine at high concentrations.

Effects on cell migration: Colchicine's antiproliferative effects were observed at 40–60 nM concentrations in all examined cell lines, every 72 hours after scratch, and at 5–20 nM concentrations in all investigated cell lines.

Effect on cell cycle: Colchicine treatment at higher concentrations resulted in a mitotic arrest in different cell lines (80% in the G2/M phase) (Balkrishna *et al*., 2019). Colchicine has antiproliferative effects by inhibiting microtubule formation by blocking the cell cycle

Colchicum autumnale

Gloriosa superb

Figure 1: Two important plant sources of Colchicine

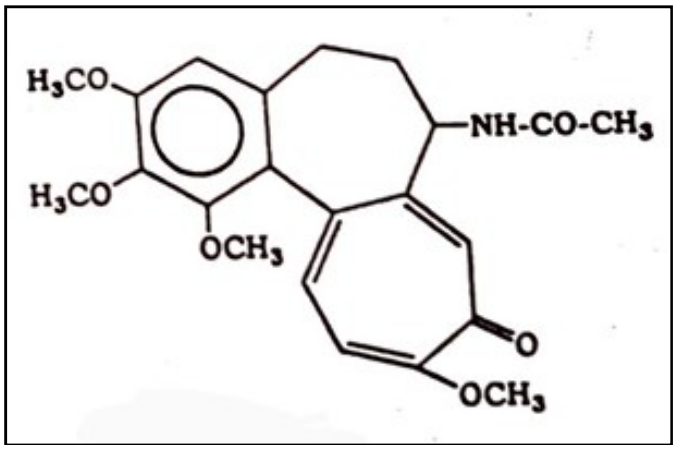


Figure 2: Chemical structure of Colchicine

at the G2/M phase and inducing apoptosis, even though it is not therapeutically used to treat cancer due to its toxicity. It merely becomes toxic at low concentrations and has no mitotic arresting properties. It can also be utilised to make several colchicine analogs, many of which have potential as anticancer drugs (Balkrishna *et al.,* 2019). The main metabolite of *Gloriosa superba* L., gloriosine, has molecular similarities to colchicine. According to recent studies,

Table 1: Biological Effect of Colchicine (Dalbeth *et al*., 2014)

Inhibits inflammatory microcrystals mediated activation of the NLRP3 inflammasome
Represses the expression of NF-κB
Reduces the number of TNF-α receptors on the surface of endothelial cells and macrophages
Make alternations to the distribution of E-selectin on the surface of endothelial cells
Inhibits MSU crystals mediated superoxide anion production
Interrupts the mast cell degranulation process
Enhances the level of TGF-β1
Reduces L-selectin expression on neutrophils

[MSU = monosodium urate; NF = nuclear factor; NLR = nucleotide-binding domain leucine-rich repeat-containing; TGF = transforming growth factor; TNF = tumor necrosis factor; Syk = spleen tyrosine kinase; TLRs = Toll-like receptors; MyD88 = Myeloid differentiation factor 88; ROS = Reactive oxygen species; (IL) -1ß = Interleukin]

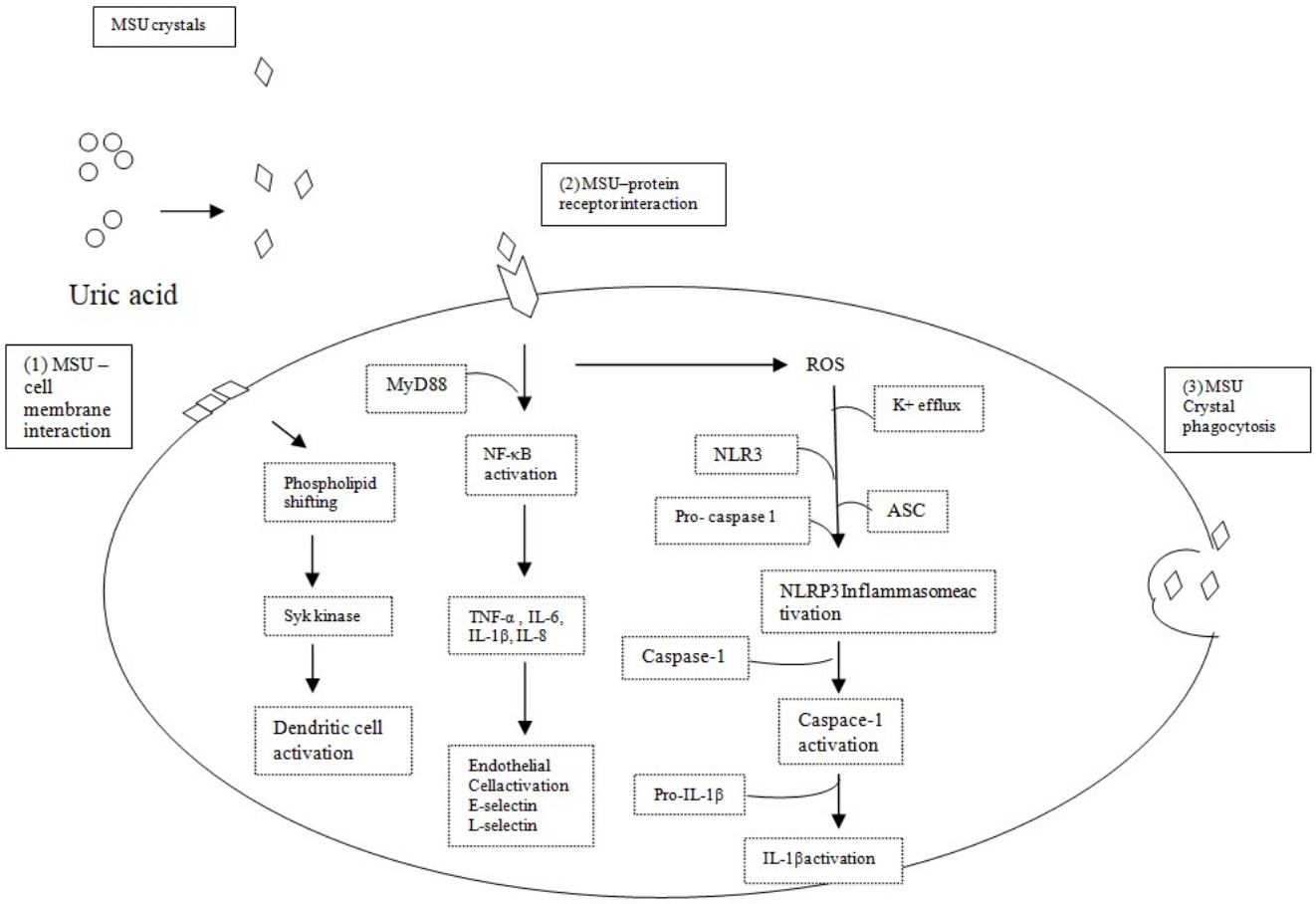
Table 2: Biological Effect of Colchicine (Leung, Yao Hui, Kraus, 2015)

Disease	Affected organ
Behcet's disease	Inflammation of the blood vessels
Chronic urticaria	Skin disease
Epidermolysis bullosa acquisita	Skin disease
Granuloma annulare	Skin disease
Henoch-Schonlein purpura	Inflammation of the blood vessels
Hidradenitis suppurative	Skin disease
Idiopathic plantar eccrine hidradentis	Skin disease
Linear IgA	Skin disease
Leukocytoclastic vasculitis	Inflammation of the blood vessels
Neutrophilic urticaria	Skin disease
Nodular vasculitis	Inflammation of the blood vessels
Purpura annularistelangiectoides	Skin disease
Pyoderma gangrenosum	Skin disease
Recurrent apthous stomatitis	Oral ulcer
Relapsing polychondritis	Cartilaginous inflammation
Scleredema	Skin disease
Scleredermadiabeticorum	Skin disease
Sweet's syndrome	Skin disease
Urticarial vasculitis	Inflammation of the blood vessels
Actinic keratosis	Skin disease
Gout arthritis	Urate crystals accumulation in joint

gloriosine can be used as a colchicine substitute in cytology and other therapeutic situations because it has a high affinity for -tubulin at CBS (Misra *et al.,* 2023).

Role of colchicine in treatment of gout

Arthritis is a chronic or acute form of joint inflammation that frequently coexists with pain and structural harm. Several types of arthritis have reported, the most common being degenerative arthritis or osteoarthritis. Inflammatory arthritis can caused by crystal deposition (basic calcium phosphate disease, gout, pseudogout), autoimmune processes (rheumatoid arthritis, psoriatic arthritis, etc.), or infections (Senthelal and Ardeshirzadeh *et al.,* 2023). Gout is a kind of inflammatory arthritis that causes swelling and severe pain in bone joints**.** Sometimes symptoms get worse, known as flares which often begin in a lower limb or big toe joint. Gout is amongst the most controllable types of arthritis if diagnosed and treated in its early stages. However, if not controlled, repeated bouts of gout can lead to gouty arthritis, an atrocious form of arthritis. Gout happens when needle-shaped crystals of monosodium urate (MSU) form around and in the bone joint due to enhanced levels of synthesis of serum urate in the body, which results in inflammation and arthritis of the joint.



When the body synthesizes too much urate or removes it very minutely, urate levels build up in body. Although many people with elevated levels of serum urate will not develop gout (CDC, 2023) (NIH, 2023).

The anti-inflammatory drug colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) like steroids and ibuprofen can treat Gout flares. Clinical trial results have shown that low-dose colchicine is effective for the treatment of acute gout flares as well as for long-term prophylactic continuation. Gout is a disease process triggered when MSU microcrystals interact with the localized tissue environment. In cases the plasma concentration of urate exceeds its solubility (~7 mg/dL), MSU crystallizes. Immunoglobulin (Ig)G and IgM, two circulating antibodies, recognize MSU crystal surfaces, stabilize them, and aid in further crystallization. Endogenous MSU crystals act as danger-associated molecular patterns (DAMPs) recognized by the innate immune system by macrophages and neutrophils. The NLRP3 inflammasome is the crucial pathway by which MSU activates the cellular inflammatory reaction. The NLRP3 inflammasome's activation, which causes the production of interleukin IL-1 and other pro-inflammatory cytokines, is a major step in the pathogenesis of gout. The arrangement of this pro-inflammatory cascade constitutes many intracellular and extracellular receptors and enzymes interacting with environmental factors which affect the inflammatory state (Dalbeth *et al*., 2014).

CONCLUSION

Gout has long been treated with colchicine, which has been around for more than a thousand years. It is the preferred method of treating amyloidosis, a consequence of familial Mediterranean Fever. Colchicine was approved as a new drug by the FDA in 2009, which had an impact on studies. The FDA has given colchicine permission to prevent gout attacks and treat acute gouty flares. Additionally, it is authorised to treat familial Mediterranean fever. Colchicine has been used off-label to treat a number of different illnesses, such as pseudogout, primary biliary cirrhosis, and hepatic cirrhosis (Sadiq, Robinson and Terrell, 2023). New uses in oncology, immunology, cardiology, and dermatology have been shown in recent studies using big cohorts of gout patients who have been taking colchicine for years. Treatment of epidermolysis bullosa acquisita, leukocytoclastic vasculitis, aphthous stomatitis, and other conditions are a few of the newly discovered dermatological applications. According to the data, colchicine inhibits many pro-inflammatory pathways by raising the number of anti-inflammatory mediators. Colchicine's pleiotropic benefits could eventually lead to its use in additional therapeutic settings. Because it was only toxic at a low quantity and didn't induce mitotic arrest, purified colchicine can also treat lung, breast, colon, pancreatic, and cervical cancer. Additional pharmacological and therapeutic research is necessary (Zhang, He, and Qin, *et al,* 2022), (Dasgeb, Kornreich and McGuinn *et al*., 2018).

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