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Role of Colchicine in the Treatment of Myocardial Infarction

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ABSTRACT

Background: Despite advances in myocardial infarction (MI) management, it remains a major global cause of morbidity and mortality, largely due to inflammation-driven cardiac remodeling and heart failure. Colchicine, a long-established anti-inflammatory drug, has emerged as a promising adjunctive therapy for MI. Clinical trials such as COLCOT and LoDoCo-MI demonstrate that low-dose colchicine after MI decreases recurrent ischemic events and cardiovascular death. However, gastrointestinal side effects and drug interactions may limit its use. This article aims to review the potential therapeutic role of colchicine in myocardial infarction, focusing on its mechanisms of action, experimental findings, and clinical outcomes. Further studies are needed to refine its optimal dosing and timing.

Conclusion: Colchicine has a therapeutic effect against MI in rats by suppression of the RAS-RAF-MAPK-ERK pathway. It alleviates myocardial remodeling and dysfunction in MI-induced rats by attenuating cardiac fibrosis, Inflammation, and apoptosis. Its mechanism also involves the inhibition of microtubule polymerization and suppression of the NLRP3 inflammasome, thereby reducing leukocyte activation, cytokine release, and myocardial damage.

Keywords: *Colchicine; Myocardial infarction; NLRP3; MI*

INTRODUCTION

Colchicine is an alkaloid that is isolated and purified from an ancient medicinal plant known as autumn crocus (or named Colchicum autumnal). It has been utilized for alleviating pain and minimizing tissue swelling [1]. Also, it has anti-inflammatory effects and is considered a potential treatment for the acute inflammatory phase of gout. In 2009, It was approved by the Food and Drug Administration (FDA) for familial Mediterranean fever (FMF) and for preventing and treating gout attacks.

More recently, colchicine has also shown therapeutic efficacy in alleviating cardiovascular complications of Coronavirus Disease (COVID-19). Clinical trials such as the cardiovascular outcomes trial (COLCOT) and the low-dose colchicine for secondary prevention of CVD trial

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(LoDoCo2) confirm the curative effect of long-term administration of colchicine in reducing the incidence of cardiovascular events in patients with coronary artery disease [2].

In June 2023, the FDA approved the use of low-dose colchicine to reduce the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease [3].

❖ *Pharmacokinetics of Colchicine:*

Colchicine is rapidly absorbed after oral administration, achieving peak plasma concentrations within approximately 3 hours in healthy adults. Its oral bioavailability is about 45%. It also has low plasma protein binding and demonstrates a large apparent volume of distribution, estimated between 5 and 8 L/kg in healthy young adults. It readily crosses the placental barrier and is excreted into breast milk. Renal excretion accounts for about 20% of colchicine clearance, while the majority is eliminated via biliary and fecal routes with significant enterohepatic recirculation. Its elimination half-life is approximately 26 to 31 hours. Colchicine undergoes extensive first-pass metabolism. It is metabolized in the intestine and liver primarily by CYP3A4 enzymes through oxidative demethylation into 2- and 3-dimethyl colchicine [4].

❖ *Mechanism of Action of Colchicine:*

➢ ***NLRP3 inflammasome:***

NLRP3 is an intracellular innate receptor that, after activation, forms the intracellular inflammasome multiprotein complex, which composed of NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1 that results in caspase 1-dependent cleavage and subsequent release of the mature inflammatory cytokines IL-1β and IL-18 [5, 6, 7]. Both IL-1β and IL-18 induce inflammation contributing to atherogenesis. Signals of pathogen-associated molecular patterns (PAPMs), damage-associated molecular patterns (DAMPs), uric acid, cholesterol crystals, and cellular debris are required to activate NLRP3 in atherogenesis **[**8, 9**]**.

Colchicine causes inhibition of the polymerization of β-tubulin microtubules (that play a crucial role in the assembly of the NLRP3 inflammasome), inhibits adhesion molecules and cytokines, and suppresses the NLRP3 inflammasome [10]. It destabilizes microtubular structures by binding to β-tubulin, which inhibits the cleavage of pro-IL-18 and pro-IL-1β into their active forms, IL-18 and IL-1β, respectively [11]. This results in decreasing endothelial inflammation, inhibiting platelet-leukocyte aggregation, and preventing atherosclerotic plaque development and destabilization [5].

➢ ***The MAPK (Ras-Raf-MEK-ERK) signaling pathway:***

Colchicine reduces reactive oxygen species (ROS) generation and inhibits oxidative stress-induced DNA damage, so it inhibits MAPK pathways and subsequently inhibits cellular senescence. This action can prevent the progression of atherosclerosis and promote atherosclerotic plaque stability [12, 13].

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Colchicine inhibits the expression of the apoptotic factor caspase-3, thereby reducing cardiac cell death [14]. Colchicine gel was reported to inhibit myocardial apoptosis and fibrosis in mice with myocardial infarction and improve cardiac function and structure [15]. Colchicine exerts its anti-inflammatory, anti-apoptotic, and anti-fibrotic effects through upregulated hepatic B-cell lymphoma 2 (Bcl-2) and downregulated Bcl-2-associated X protein (BAX) expression and transforming growth factor-β (TGF-β) content, which attenuates rat liver injury induced by renal ischemia-reperfusion injury [16].

❖ *Uses of Colchicine:*

Colchicine is used in multiple diseases such as **dermatological diseases** (psoriasis, scleroderma, dermatitis herpetiformis, vasculitis, acne and bullous dermatosis) [17], **crystal-induced arthropathy** (gout, and pseudogout), **cardiac diseases** (acute pericarditis, chronic relapsing pericarditis, prevention of coronary artery disease, and prevention of post-operative atrial fibrillation), and **other miscellaneous diseases** (familial mediterranean fever (FMF), Bechet disease, amyloidosis, sweet syndrome, and sarcoidosis) [18].

Also, colchicine was associated with a reduction in overall mortality of COVID-19 patients according to an umbrella review of published meta-analyses published in September 2023. However, it remains uncertain if this effect could potentially be attenuated or augmented by COVID-19 vaccination [19].

❖ *Dosage and administration:*

Colchicine has demonstrated effectiveness in preventing acute inflammatory flares in many diseases. In patients with Familial Mediterranean Fever (FMF), the highest maintenance doses (up to 2.4 mg daily) are utilized to prevent inflammatory attacks and renal amyloidosis [20]. Conversely, lower maintenance doses, typically 0.5–0.6 mg administered twice daily, are commonly prescribed for conditions such as Behçet's disease, gout flares, and recurrent pericarditis and have recently been associated with a reduction in cardiovascular events among patients with established coronary artery disease [21, 22].

Recent evidence, however, indicates that colchicine 0.5 mg daily is better tolerated and equally effective as 0.5 mg twice daily for preventing gout flares during the initiation of urate-lowering therapy [23].

❖ *The Safety Profile of Colchicine:*

Colchicine is characterized by a narrow therapeutic index, with poorly defined boundaries between non-toxic, toxic, and lethal doses. This significantly limits its clinical use due to its toxicity [24]. It is generally well tolerated when administered at age-dependent doses, not exceeding 2 mg per day in children (≤12 years) and 3 mg per day in adults with normal hepatic and renal function. Tolerability is maintained provided that no concomitant medications are used that could alter its pharmacokinetics [25].

❖ *Overdose toxicity:*

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Colchicine exhibits dose-dependent toxicity [26]. Doses of 0.5–0.8 mg/kg are considered highly toxic, and doses exceeding 0.8 mg/kg are typically fatal [27]. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and diarrhea are common which resulting from mucosal injury and a cholera-like syndrome [28]. The primary cause of death is multi-organ failure. Within 10–24 hours post-ingestion, patients often present with gastroenteritis-like symptoms (absent in intravenous users), followed by multi-organ involvement from 24 hours to 7 days, with recovery typically occurring after one week [29]. There are no specific treatments for colchicine poisoning, so management relies on supportive care. Observation is essential during the first 24 hours, as symptoms are unlikely to appear after this period. Early administration of activated charcoal or gastric lavage may reduce its absorption, although vomiting can limit their use [30].

Attempts to eliminate colchicine using haemodialysis or plasma exchange have limited success due to its short half-life and high tissue binding. While colchicine is 40–50% protein-bound at therapeutic levels, plasma exchange has shown minimal removal (0.01% of ingested dose), casting doubt on its clinical utility [31], although other reports have suggested potential benefit. Haemodialysis is mainly supportive in cases of renal impairment [32].

Favorable outcomes have been shown from animal studies using colchicine-specific antigen-binding fragments (Fab), and human cases treated with Fab fragments have been documented [33,34].

REFERENCES

1. Chaldakov GN. Colchicine, a microtubule-disassembling drug, in the therapy of cardiovascular diseases. Cell Biol Int. 2018;42(8):1079–84.
2. Zhang FS, He QZ, Qin CH, Little PJ, Weng JP, Xu SW. Therapeutic potential of colchicine in cardiovascular medicine: A pharmacological review. Acta Pharmacol Sin. 2022;43(9):2173–90.
3. U.S. Food and Drug Administration. NDA approval (215727); June 2023. Available at www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/215727Orig1s000ltr.pdf.
4. Sadiq NM, Robinson KJ, Terrell JM. Colchicine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Nov 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431102/
5. Grebe A, Hoss F, Latz E. NLRP3 inflammasome and the IL-1 pathway in atherosclerosis. Circ Res. 2018;122:1722–40.
6. Swanson KV, Deng M, Ting JPY. The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. Nat Rev Immunol. 2019;19:477–89.
7. Silvis MJM, Demkes EJ, Fiolet ATL, et al. Immunomodulation of the NLRP3 inflammasome in atherosclerosis, coronary artery disease, and acute myocardial infarction. J Cardiovasc Transl Res. 2020;13(3):431–45.
8. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature. 2010;464(7293):1357–61.
9. Kim SK. The mechanism of the NLRP3 inflammasome activation and pathogenic implication in the pathogenesis of gout. J Rheum Dis. 2022;29(3):140–53.
10. Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis. 2018;269:262–71.
11. Pennings GJ, Reddel CJ, Traini M, Campbell H, Chen V, Kritharides L. Colchicine inhibits ROS generation in response to glycoprotein VI stimulation. Sci Rep. 2021;11(1):11965.

10.48047/jocaaa.2024.33.06.149

12. Song P, Zhao Q, Zou MH. Targeting senescent cells to attenuate cardiovascular disease progression. Ageing Res Rev. 2020;60:101072.
13. Sun X, Duan J, Gong C, Feng Y, Hu J, Gu R, et al. Colchicine ameliorates dilated cardiomyopathy via SIRT2-mediated suppression of NLRP3 inflammasome activation. J Am Heart Assoc. 2022;11(13):e025266.
14. Pappritz K, Lin J, El-Shafeey M, Fechner H, Kühl U, Alogna A, et al. Colchicine prevents disease progression in viral myocarditis via modulating the NLRP3 inflammasome in the cardiosplenic axis. ESC Heart Fail. 2022;9(2):925–41.
15. Chen Y, Shi J, Zhang Y, Miao J, Zhao Z, Jin X, et al. An injectable thermosensitive hydrogel loaded with an ancient natural drug colchicine for myocardial repair after infarction. J Mater Chem B. 2020;8(5):980–92.
16. Awad AS, Elariny HA, Sallam AS. Colchicine attenuates renal ischemia-reperfusion-induced liver damage: Implication of TLR4/NF-κB, TGF-β, and BAX and Bcl-2 gene expression. Can J Physiol Pharmacol. 2022;100(1):12–8.
17. Dastoli S, Nistico SP, Morrone P, Patruno C, Leo A, Citraro R, et al. Colchicine in managing skin conditions: A systematic review. Pharmaceutics. 2022;14(2):294.
18. Schattner A. Colchicine – New horizons for an ancient drug: Review based on the highest hierarchy of evidence. Eur J Intern Med. 2022;96:34–41.
19. Danjuma MI, Sayed R, Aboughalia M, Hassona A, Elsayed BS, Elshafei M, et al. Does colchicine reduce mortality in patients with COVID-19 clinical syndrome? An umbrella review of published meta-analyses. Heliyon. 2023;9(10):e21537.
20. Robinson PC, Terkeltaub R, Pillinger MH, Shah B, Karalis V, Karatza E, et al. Consensus statement regarding the efficacy and safety of long-term low-dose colchicine in gout and cardiovascular disease. Am J Med. 2022;135(1):32–8.
21. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–505.
22. Nidorf SM, Fiolet AT, Mosterd A, Eikelboom JW, Schut A, Opstal TS, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838–47.
23. Ahn SM, Oh JS, Hong S, Lee CK, Yoo B, Kim YG. Comparative efficacy of low-dose versus regular-dose colchicine to prevent flares in gout patients initiated on urate-lowering therapies. Rheumatology (Oxford). 2022;61(1):223–9.
24. Mitev V. What is the lowest lethal dose of colchicine? Biotechnol Biotechnol Equip. 2023;37(1):2288240.
25. Ben-Chetrit E. Colchicine. In: Hashkes P, Laxer R, Simon A, editors. Textbook of autoinflammation. Cham: Springer; 2019. p. 1–14.
26. Roddy E, Mallen CD. Colchicine in overdose. Br J Gen Pract. 2017;67(655):61.
27. Slobodnick A, Shah B, Pillinger MH, Krasnokutsky S. Colchicine: Old and new. Am J Med. 2015;128(5):461–70.
28. Rahimi M, Alizadeh R, Hassanian-Moghaddam H, Zamani N, Kargar A, Shadnia S. Clinical manifestations and outcomes of colchicine poisoning cases: A cross-sectional study. Arch Acad Emerg Med. 2020;8(1):e53.
29. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, et al. Colchicine poisoning: The dark side of an ancient drug. Clin Toxicol (Phila). 2010;48(5):407–14.
30. Stamp LK, Horsley C, Te Karu L, Dalbeth N, Barclay M. Colchicine: The good, the bad, the ugly and how to minimize the risks. Rheumatology (Oxford). 2024;63(4):936–44.
31. Wacker M, Pietsch J, Okrojek R. Effect of plasma exchange on colchicine elimination in overdose—A case report. Clin Toxicol (Phila). 2021;59(8):849–50.
32. Schaffer DH, Overbeek DL, Erickson TB. Severe colchicine poisoning treated successfully with kidney replacement therapy and plasmapheresis: A case report. Toxicol Commun. 2022;6(1):47–51.
33. Baud FJ, Sabouraud A, Vicaut E, et al. Treatment of severe colchicine overdose with colchicine-specific Fab fragments. N Engl J Med. 1995;332(10):642–5.
34. Eddleston M, Fabresse N, Thompson A, et al. Anti-colchicine Fab fragments prevent lethal colchicine toxicity in a porcine model: A pharmacokinetic and clinical study. Clin Toxicol (Phila). 2018;56(8):773–81.