



Review Article

The Role of Colchicine in Acute Coronary Syndrome

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ABSTRACT

Background: Despite the advances of current optimal treatment of atherosclerotic disease, the incidence of events after acute coronary syndrome (ACS) remains high. Colchicine, with its well-established pleiotropic anti-inflammatory effects, may inhibit NLRP3 inflammasome, a key mediator in atherosclerosis-associated inflammation (AAI) thus reducing systemic inflammation. NLRP3 inflammasome activation inside leukocytes (mainly monocytes and neutrophils) is precipitated by cholesterol crystals that are present in all atherosclerosis stages. Subsequent activation of pro-inflammatory cytokines such as interleukin-1 β and interleukin-18 will follow. These cytokines are the crucial inflammatory pathway mediators that promote the formation of plaque and instability in the inflammatory cascade.

Objective: This review will elaborate on the function of immune cells in atherosclerosis, explain the mechanisms of NLRP3 inflammasome activation in the context of AAI, and address the possible role of colchicine specifically targeting NLRP3 inflammasome and its concomitant downstream mediators in ACS, and provide an overview of current or ongoing studies produced in this area.

Discussion : NLRP3 inflammasome activation inside leukocytes (mainly monocytes and neutrophils) is precipitated by cholesterol crystals that are present in all atherosclerosis stages. Subsequent activation of pro-inflammatory cytokines such as interleukin-1 β and interleukin-18 will follow. These cytokines are the crucial inflammatory pathway mediators that promote the formation of plaque and instability in the inflammatory cascade. A potential advantage of a medication acting through an inflammatory milieu found in atherosclerotic lesions has recently become the need for novel therapeutic options. Colchicine, with its well-established pleiotropic anti-inflammatory effects, may inhibit NLRP3 inflammasome, a key mediator in atherosclerosis-associated inflammation (AAI) thus reducing systemic inflammation.

Conclusion: Colchicine is a safe and reliable medication for ACS patients, alongside reveal various benefit in reducing inflammation through inhibition of NLRP3 Inflammasome.

1. Introduction

Inflammation in acute coronary syndrome (ACS) occurs in multiple pathways. Nucleotide-binding Oligomerization Domain-Like Receptors, Pyrin Domain-Containing 3 (NLRP3) inflammasome has been known to serve as a key mediator in atherosclerotic plaque formation, progression, and destabilization.¹ The risk of recurrent major cardiovascular events (up to 20% at 3 years) is increased in patients with an index ACS, indirectly explained by lingering coronary inflammation at the culprit and non-culprit sites after prior ACS episode, despite current guideline-based medical treatment.² Colchicine is a safe, simple, low-cost, yet potent anti-inflammatory medication widely known for the treatment of acute gout, and other cardiac conditions such as pericarditis, which may represent another potential role of inflammation in ACS. The mechanisms of colchicine in manipulating leukocytes include its ability to suppress NLRP3 inflammasome through impairment of mitochondrial colocalization of inflammasome proteins,

disruption of microtubule formation, and inhibition of inflammasome activation and cytokine production.³ This review outlines the action of colchicine as a secondary preventive agent after index ACS and elucidates an overview of trials currently develop this far.

2. NLRP3 Inflammasome and Inflammation in ACS

The pathogenesis of the development, growth, and rupture of atherosclerotic plaque is primarily linked to inflammation, contributing to acute clinical incidents. Both innate and adaptive immune systems are involved in inflammation. Mononuclear phagocytes (monocytes and macrophages) play a significant role in the inflammatory response in the whole atherosclerotic disease process, present from atherogenesis, plaque formation, destabilization, and rupture, and subsequently in the healing process after acute infarction as the key effectors. Monocyte recruitment started in the early stages of atherosclerosis, then continues in mature plaque formation, suggesting

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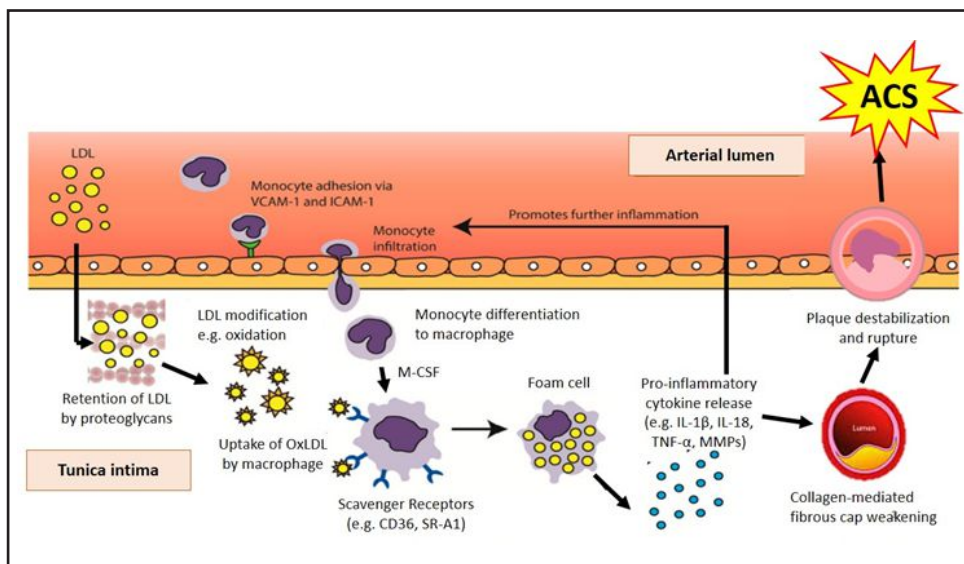


Figure 1. Inflammatory pathway in acute coronary syndrome.⁴

Infiltration of low-density lipoprotein (LDL) and formation of macrophage foam cells in arterial wall leading to the release of pro-inflammatory cytokines, which further contributes to plaque destabilization and subsequent rupture, presenting as an acute coronary syndrome.

continuous activation in many phases of plaque development. In the early phases, phagocytosis of oxidized Low-Density Lipoproteins (ox-LDL) by macrophages mediated by scavenger receptor A and CD36 as a membrane receptor, promoting secretion of several cytokines, such as interleukin-1 β (IL-1 β) and TNF- α , thus transform itself into foam cells. Monocytes/macrophages activation further release metalloproteinases, which destabilize the plaque through the weakening of collagen-mediated fibrous cap in the later phase of plaque development, which in turn may result in plaque rupture and subsequently, Myocardial Infarction.²

To respond to harmful or pathogenic signals, the innate immune response relies heavily on Pattern-Recognition Receptors (PRRs). Inflammasomes are one such cytoplasmic PRR. It is a Pyrin domain-containing 3 Nucleotide-binding Oligomerization Domain (NOD)-like receptor (or NLR for short) (NLRP3; which also named NALP3 or cryopyrin). In all myeloid cells, including eosinophils, neutrophils, and monocytes, NLRP3 is present.^{2,4}

Formerly recognized as a type of Toll-like receptor (TLR) NLRP3 is part of the family of NOD-like receptors (NLR), while transmembrane innate immune sensors are TLRs. NLRP3 is not a form of TLR, whereas both TLR and NLR are PRRs containing a leucine-rich repeat domain. TLRs and NLRs differ partly in downstream signaling pathways, activation mechanism, cellular localization, and domain composition.⁴ The NLRP3 inflammasome comprises 3 main components i.e.: 1) NLRP3 receptor (a type of TLR); 2) Caspase-Containing and Activation Recruitment Domain (CARD) Apoptosis-Associated Speck-Like Protein-ASC as an adaptor protein; and 3) Caspase-1 as the effector cysteine protease. However, ASC plays a role as the link between NLRP3 and caspase-1 since it lacks a pyrin domain.⁵

Activation of inflammasome complex is explained following increase reactive oxygen species (ROS) and large molecule damage-associated molecular pattern (DAMP) exposure, such as cholesterol crystals. Inefficient removal after phagocytosis of DAMP results in lysosome destabilization and subsequent rupture. This later releases cathepsin B into the cytoplasm and stimulates the development of the inflammasome complex and its inflammatory cytokines downstream. Normally, inflammatory components (NLRP3 receptors, caspase-1, and ASC) and their substrates (pro-IL-1 β and pro-IL-18) are identified at

very low levels. Hence, inflammasome activation requires a two-step process. First, initial priming is triggered by TLR stimuli or monocyte interaction, as it will be elucidated later, which leads to the nuclear factor kappa B (NF- κ B) activation, which promotes inflammasome components transcription. Second, additional stimuli start the assembly of inflammasome and activation of Caspase-1, resulting in the production of cytokine.^{5,6}

Activation of inflammasome has been linked with damage of myocardium following infarction and subsequent reperfusion. A previous clinical study of ACS patients demonstrated a higher level of NLRP3, cathepsin-B, IL-18, and IL-1 β compared to normal controls.⁷ A previous in vivo analysis found that the ASC and caspase-1 deficiency in mice models led to a decline in inflammation, duration of infarction, and myocardial fibrosis following ischemia.² Activation of inflammasome appears to be the main mechanism to explain the monocytes/macrophages and PMN mutual interaction. It is understood that PMN granule secretion draws monocytes to the location of atherosclerotic plaque, further encouraging plaque progression and vulnerability. Besides, neutrophils may stimulate monocyte production of IL-1 β and IL-18, key cytokines that have been linked to atherogenesis. IL-1 β and IL-18 are produced as inactive forms and need the cleavage of caspase-1 mediated by NLRP3 inflammasome to create the active form. Either IL-1 β or IL-18 enhances chemokines release that further attracts neutrophils into the atherosclerotic unstable plaques.⁸

Martinez et al. (2015) demonstrated that in atherosclerosis patients inflammasome end-products IL-1 β and IL-18 are expressed locally. Levels of these two cytokines depend on the activity of the disease. ACS patients exhibited the highest trans-coronary gradients, The second highest gradient in patients with stable angina, and the lowest gradient in patients with non-obstructive coronary artery disease. IL-1 β can also influence post-MI cardiac remodeling in addition to its role in atherosclerosis. Inhibition of IL-1 β involvement inhibits post-MI apoptosis and fibrosis, thereby improving myocardial malfunction and negative remodeling.¹

3. NLRP3 Inflammasome Inhibition Function of Colchicine

Colchicine is a low-cost drug that is safe and globally available. Colchicine is used mostly as gouty arthritis and treatment for

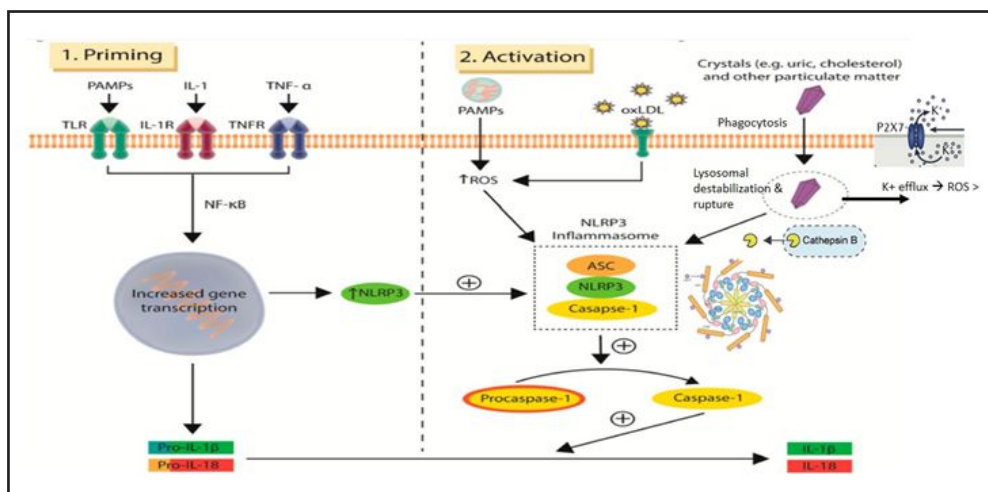


Figure 2. Two-signal activation of NLRP3 inflammasome.⁴

Activation of the NLRP3 inflammasome requires both the initial priming step (left) and the following activation step (right). Priming of macrophages is provided by endogenous cytokines (IL-1 and TNF- α) and binding of PAMPs on damage large molecules to membrane-bound TLR. The second activation step involves a variety of stimuli, including intracellular oxLDL accumulation, PAMPs, and crystalline particulates such as uric and cholesterol crystals. The NLRP3 inflammasome catalyzes the conversion of pro-caspase-1 to its active form, caspase-1, which then converts pro-IL-1 β and pro-IL-18 into their bioactive, pro-atherogenic forms, IL-1 β and IL-18.

familial Mediterranean fever. Colchicine is commonly recommended in cardiology as an anti-inflammatory treatment for both chronic and acute pericarditis. Colchicine has a potent but relatively safe anti-inflammatory function in contrast to other immunosuppressive agents, which attracts its implementation as a medication for inflammatory diseases.² Colchicine acts on mitosis by promoting depolymerization of the microtubule by binding to tubulin. Colchicine thus inhibits many microtubule functions: chromosome pair separation during mitosis, leucocyte amoeboid movements including exocytosis and phagocytosis. Colchicine inhibits COX-2 production as well as TNF- α , leukotriene B₄, prostaglandin E₂, and TxA₂ production. Reducing the expression of both E and P-selectin, colchicine disrupts adhesion of PMN to endothelium which interrupts neutrophil migration, thus inhibits inflammation, even at low doses.⁹

More recently, NLRP3 inflammasome activity inhibition has been identified to be associated with a novel mechanism of action, thus suppressing cytokine output (IL-1 β and IL-18) and neutrophil migration. Another presumed mechanism of action by which colchicine may inhibit the activation of inflammasome NLRP3 is the suppression of pyrin (MEFV) gene expression, a gene that codes for the NLRP3 receptor, impairing the assembly of NLRP3 inflammasome. It is known, recently, that monocyte caspase-1 inhibition is the colchicine mechanism of action in ACS patients.² In contrast, Misawa et al. (2013) demonstrated colchicine inhibition of intracellular ASC transport by blocking co-localization and action of NLRP3 inflammasome proteins.¹⁰ Colchicine impairs the mobilization of CARD – ASC, to the endoplasmic reticulum from the mitochondria. This in turn prevents its co-localization with the rest of the inflammasome complex.¹ Colchicine induces effective inhibition of pore formation caused by P2X7 (which is the key step in the inflammasome response of NLRP3 to ATP), resulting in lower levels of IL-1 β and ROS.²

Considering these novel effects on the NLRP3 inflammasome, also the well-known actions on neutrophil migration, microtubular function, and colchicine has arisen as a plausible future approach for the treatment of diseases mediated by atherosclerosis, particularly acute coronary syndromes.

PROSPECT Trial demonstrated the additional therapy is crucial in patients with ACS by assessing the natural history of 697 patients hospitalized with ACS who underwent successful uncomplicated percutaneous transluminal coronary angioplasty (PTCA). After a follow-up period of 3 years, the cumulative risk of MACE was <1%, 15%, and 20.4% at 30 days, 12 months, and 3 years respectively. almost half of the events related to the progression of non-culprit lesions (NCL) in the first year. However, beyond the first-year clinical events were twice as likely to relate to the NCL progression. NCL had a large lipid-rich vulnerable plaque burden and a thin fibrous cap when assessed by intravascular ultrasound. NCL often contains cholesterol crystals in high concentrations, which may be potential in NLRP3 inflammasome activation. Colchicine has been shown to prevent and dampen this mechanism.¹¹

In 532 patients with healthy coronary artery disease, the Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease Study (LoDoCo Trial) stated that long-term colchicine treatment (0.5 mg/day) resulted in a 3-year improvement in acute events relative to no colchicine treatment.^{1,12} Based on this result, many trials are developed to determine the action of colchicine in the ACS setting, regarding its anti-inflammatory properties. Hence, the Low Dose Colchicine after Myocardial Infarction (LoDOCo-MI) Study was conducted as a sequel to the previous trial which commences the subset of AMI patients. This was a randomized, double-blind study of 237 acute MI patients using low-dose colchicine (0.5 mg daily) or matching placebo. The primary outcome in this study was the proportion of patients with a residual high sensitivity C-reactive protein (CRP) level ≥ 2 mg/L after thirty days of therapy. It was shown by LoDoCo-MI that low-dose colchicine was safe and quite well tolerated. However, the likelihood of achieving a lower absolute CRP level in 30 days or CRP level < 2 mg/L after an acute infarction was not significantly increased.¹²

The Colchicine Cardiovascular Outcomes Trial (COLCOT Study) was performed over 4745 patients surviving 30 days after an acute MI. They were randomly divided into colchicine versus the placebo group, half in amount among each group. The primary endpoint was a major adverse cerebrocardiovascular event (MACCE) and urgent rehospitalization for angina leading to coronary revascularization during 2-year follow-up. This study demonstrated that among patients with a recent myocardial infarction, low-dose colchicine at a

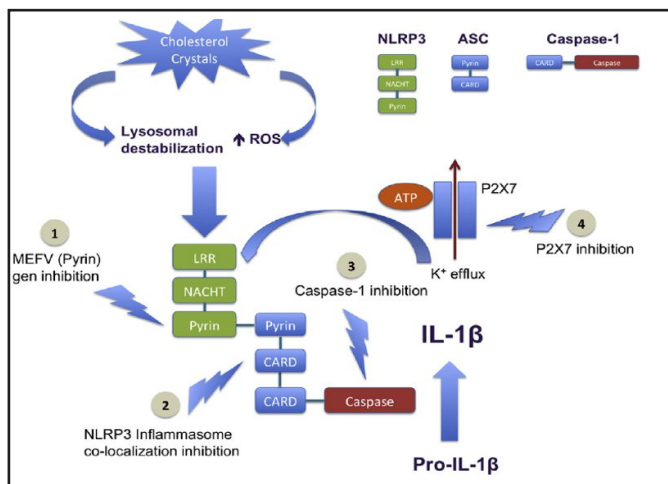


Figure 3. Colchicine inhibition of the NLRP3 inflammasome.²

At least four purported mechanisms of inhibition of the NLRP3 inflammasome by colchicine have been described. 1) Inhibition of MEFV gene resulting in Pypin (receptor) inhibition; 2) inhibition of inflammasome cytoplasmic co-localization due to tubulin interference; 3) direct caspase-1 blockage; 4) inhibition of P2X7-mediated pore formation resulting in decreased K⁺ efflux. The final result is inhibition of active form IL-1 β (and probably IL-18) production.

dose of 0.5mg daily led to a significantly lower risk of ischemic MACCE and urgent rehospitalization (5.5% and 7.1%, respectively) compared to placebo on top of contemporary optimal medical treatment (OMT). Time-to-Treatment Initiation (TTI) of low-dose colchicine within days 0-3 after MI significantly reduces the risk of ischemic CV events by 48% compared to placebo, but not statistically significant within TTI days 4-7 and days 8-30 after MI. This study elucidated a subgroup analysis of these population who underwent PCI (4408 patients) and revealed that administration of low-dose colchicine daily after PCI for MI reduced risk of MACCE and rehospitalization for urgent revascularization (5.2% and 7.1%, respectively) compared to placebo. Early initiation of colchicine, within 3 days following PCI for an MI, reduced the risk of ischemic CV events by 40%, as well.¹³

Colchicine was prescribed to 44 patients hospitalized for ST-segment elevation myocardial infarction (STEMI) in patients with acute myocardial infarction (COLIN trial) who were treated successfully with the percutaneous coronary intervention (PCI). They were divided in half amount into colchicine (as an addition to optimal medical treatment) group versus control (conventional optimal medical treatment only) group. The treated group was given colchicine 1mg once daily for one month, with no loading dose. On admission, baseline CRP was taken and proceeded daily until discharge. During the index hospitalization, the CRP peak value was set as the primary endpoint. The outcome seen in this research was no significant difference in mean CRP peak value relative to the control group of colchicine administration.¹⁴

A prospective randomized study - Anti-Inflammatory Treatment with Colchicine in Acute Myocardial Infarction: A Pilot Study, held by Defteros et al. (2015), was comparing the administration of colchicine or placebo for 5 days in 151 STEMI patients presenting \leq 12 hours from pain onset (treated with primary PCI). The result demonstrated that the administration of oral colchicine (loading dose of 2 mg and continuing with 0.5mg twice daily) was correlated with smaller infarct size, as defined by a reduction in area under the curve of creatine kinase-MB and in infarct size on cardiac MRI, as well as a reduction in post-myocardial-infarction inflammatory markers such as neutrophil count and CRP which is known to be strongly related to infarct size.¹⁵

Robertson et al. (2016) studied 21 ACS patients who were randomized to oral colchicine (1mg followed by 0.5mg 1 hour later) or no treatment and compared with 9 untreated healthy control. NLRP3 inflammasome markers (pro-caspase-1 mRNA level and caspase-1 protein), IL-1 β , and IL-18 levels were the key endpoints. In ACS patients, levels of IL-1 β and IL-18 were slightly higher. Colchicine therapy in ACS patients substantially lowered secreted and intracellular IL-1 β levels reduced significantly pro-caspase-1 mRNA levels and secreted caspase-1 protein levels relative to untreated patients. In ACS patients, Inflammasome-related cytokines are primed to be secreted by monocytes. Moreover, colchicine administered in short-term acutely and significantly inhibits the activity of monocyte caspase-1, thus reducing IL-1 β monocyte secretion.¹⁶

Martinez et al. (2015) studied 40 ACS patients, 33 with stable CAD, and 10 controls in a randomized control trial. Patients are grouped into either oral colchicine treatment (1mg followed by 0.5mg 1 hour later) group or no colchicine group, 6 to 24 hours before DCA. IL-1 β , IL-6, and IL-18 levels collected from the coronary sinus, aortic root (arterial), and lower right atrium (venous) blood were the main endpoints. In ACS patients, coronary sinus levels of IL-1 β , IL-6, and IL-18 were found to be substantially higher than arterial and venous levels. IL-1 β , IL-6, and IL-18 transcoronary (coronary sinus-arterial) gradients were highly expressed in ACS patients and lowest in controls. Administration of colchicine in ACS patients markedly reduced trans coronary gradients of all cytokines by 40% to 88%. ACS patients exhibit an enhanced local cardiac synthesis of inflammatory cytokines, which are rapidly reduced by the short-term administration of colchicine.¹ It has been suggested that the supposed mechanisms by which colchicine prevents the release of these inflammatory cytokines correlate with the inflammasome complex activation block explained above. Colchicine is indicated to exert its beneficial effects across various mechanisms on the inflammasome complex. For example, as seen in the previous report, it can rapidly suppress the assembly of the inflammasome complex, thereby exerting an acute effect. It may also have a transcriptional effect, a mechanism related to longer exposure to the drug, which further impairs the synthesis of IL-1 β and IL-18.

The Acute Colchicine Administration Before PCI (COLCHICINE-PCI Randomized Trial) was performed among 400 subjects who underwent PCI, which was randomized to acute preprocedural (1-2 hours before PCI) oral administration of colchicine 1.8mg or placebo. The result demonstrated acute preprocedural administration of colchicine attenuated the elevation of interleukin-6 and high-sensitivity C-reactive protein concentrations, but not the increase of IL-1 β , 24-hours after PCI when compared with placebo. Colchicine decreased inflammation 24-hours post-PCI (prevented a rise in inflammation during acute injury) but did not reduce the risk of PCI-related myocardial injury or 30-days MACE when compared with placebo.¹⁷

The latest on-going study, the Colchicine to Improve Cardiovascular Outcomes in ACS Patients (COPS Trial), included 795 patients hospitalized for ACS who have undergone diagnostic coronary angiography (DCA) with $>$ 30% stenosis and have been treated with PCI or conservatively. The study population was classified into two groups, ie. colchicine plus OMT versus placebo plus OMT group. The former group was given an oral low dose of 0.5mg colchicine twice a day for 4 weeks followed by 0.5mg daily for 11 months. The primary composite endpoints included all-cause mortality, recurrent ACS, stroke, and urgent target vessel revascularization for angina were assessed during 12-months, 2-year, and 5-year follow up. The result revealed that low-dose oral colchicine in addition to OMT during hospitalization and continued for 12-months was associated with a lower rate of the primary composite outcomes for at least 400 days after the index hospitalization. Longer-term follow-up of the COPS cohort is planned.¹⁸

5. Conclusion

The pathogenesis of atherosclerotic plaque formation, progression, and rupture is mainly associated with inflammation, leading to acute clinical events. Monocytes/macrophages and neutrophils are key effectors of the inflammation occurred during acute coronary syndrome. NLRP3 inflammasome, a pattern-recognition receptor, which commonly presents in myeloid cells, is found to play important role in atherosclerosis-mediated inflammation. NLRP3 inflammasome and the synthesis of its downstream inflammatory cytokines are activated following increase reactive oxygen species (ROS) and large molecule damage-associated molecular pattern (DAMP) exposure, such as large cholesterol crystals, found in the progression of atherosclerosis. Colchicine, an ancient anti-inflammatory drug, is known for its pleiotropic effects, which could inhibit the action of NLRP3 inflammasome and its downstream inflammatory cytokines through several mechanisms, either in patients with stable CAD or ACS. Many trials have been studied about the beneficial role of colchicine in the ACS settings, either in the short- or long-term benefit of its anti-inflammatory properties as well as reducing the subsequent MACE. This review is directed to encourage future studies in favor of this ancient, yet recently re-emerging drug, to lower the rate of recurrent cardiovascular events and improve patient outcome.

6. Declarations

4.1. *Ethics Approval and Consent to participate*
Not applicable.

4.2. *Consent for publication*
Not applicable.

4.3. *Availability of data and materials*
Data used in our study were presented in the main text.

4.4. *Competing interests*
Not applicable.

4.5. *Funding source*
Not applicable.

4.6. *Authors contributions*
Idea/concept: HAR. Control/supervision: BS. Literature review: HAR. Writing the article: HAR. Critical review: BS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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