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Colchicine --- update on mechanisms of action and therapeutic uses

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Abstract

Objectives—To review the literature and provide an updates on the mechanisms of action and therapeutic uses of oral colchicine in arthritis and inflammatory conditions.

Methods—We performed PubMed database searches through June 2014 for relevant studies in the English literature published since the last update of colchicine in 2008. Searches encompassed colchicine mechanisms of action and clinical applications in medical conditions. A total of 381 articles were reviewed.

Results—The primary mechanism of action of colchicine is tubulin disruption. This leads to subsequent down regulation of multiple inflammatory pathways and modulation of innate immunity. Newly described mechanisms include various inhibitory effects on macrophages including the inhibition of the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome, inhibition of pore formation activated by purinergic receptors P2X7 and P2X2, and stimulation of dendritic cell maturation and antigen presentation. Colchicine also has anti-fibrotic activities and various effects on endothelial function. The therapeutic use of colchicine has extended beyond gouty arthritis and Familial Mediterranean Fever, to osteoarthritis, pericarditis and atherosclerosis.

Conclusion—Further understanding of the mechanisms of action underlying the therapeutic efficacy of colchicine will lead to its potential use in a variety of conditions.

Keywords

colchicine; mechanism of action; inflammation; pharmacokinetics; therapeutic use

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Conflict of interest

There is no conflict of interest in regard to the content of the manuscript.

1. INTRODUCTION

Colchicine is an alkaloid extracted from plants of the genus Colchicum (autumn crocus). The therapeutic use of colchicine has been well documented in gout and familial Mediterranean fever (FMF); it has also been used in other diseases including Behcet's disease (BD), pericarditis, coronary artery disease and other inflammatory and fibrotic conditions. The pharmacotherapeutic mechanism of action of colchicine in diverse disorders is not fully understood. The aim of this article is to review the literature and provide an update on the mechanisms of action and therapeutic uses of colchicine in various inflammatory conditions.

2. METHODS

We performed a PubMed database search for relevant studies published using the search terms "mechanism of action" OR "inflammation" OR "pharmacokinetics" OR "toxicity" OR "therapeutic use" AND "colchicine" between 1st Jan 2008 to 15th June 2014 and restricted to the English language. The start date was chosen to cover literature published since the topic was last comprehensively reviewed in 2008 [1][2] We focused on original articles that provided new information on the mechanisms of action of colchicine in various conditions and clinical applications of colchicine in medical conditions. Additionally, references noted in relevant articles were also reviewed. A total of 1,705 articles published in English were identified from the PubMed search and 1,354 of these articles were deemed to be outside the scope of this review. A total of 351 relevant articles from the search and 30 articles from relevant references were retrieved for full text review. The final review included 116 articles on mechanisms of action, 23 articles on pharmacokinetics and toxicities, 39 articles on therapeutic uses, 80 review articles, 49 observational studies, and 74 case reports.

3. RESULTS

3.1 Mechanism of action

3.1.1 Tubulin Disruption and anti-mitotic effect of colchicine—The most studied therapeutic mechanism of action of colchicine is its capacity to bind to tubulins, thereby blocking the assembly and polymerization of microtubules. Microtubules, key components of the cytoskeleton, are made up of αβ-tubulin heterodimers. Microtubules are involved in various cellular processes including maintenance of cell shape, intracellular trafficking, cytokine and chemokine secretion, cell migration, and regulation of ion channels and cell division. Colchicine is a classical anti-mitotic drug which blocks mitotic cells in metaphase. It binds to soluble tubulin to form tubulin-colchicine complexes in a poorly reversible manner, which then binds to the ends of microtubules to prevent the elongation of the microtubule polymer. At low concentrations, colchicine arrests microtubule growth and, at higher concentrations, colchicine promotes microtubule depolymerisation. It causes severe toxicity to normal tissues at high dose, which limits its use in cancer therapies [3]. Although none has yet developed to the point of clinical application in anticancer therapy, numerous compounds with the capability of interacting with the colchicine binding site have been described over the last decade [4]. Other effects of colchicine on malignancy include inhibition of cancer cell migration and metastatic potential [5], cell blebbing via a Rho/ Rho

effector kinase (ROCK)/myosin light chain kinase (MLCK) pathway [6], inhibition of angiogenesis [7], limitation of adenosine triphosphate (ATP) influx into mitochondria [8] and release of cysteine-dependent aspartate-directed proteases (caspases) and cytochrome-c, leading to apoptotic cell death [3]. Colchicine also has anti-inflammatory effects, mainly related to disruption of microtubules and downstream cellular functions of leucocytes. Figure 1 summarizes the main anti-inflammatory mechanisms of action of colchicine.

3.1.2 Mechanisms of action of colchicine on the immune system—Recent advances in the understanding of the pathophysiology of crystal-induced inflammation, summarized by Nuki et al [1], have provided new insights into the mechanisms of action of colchicine in crystal arthropathies. The main mechanisms are inhibition of neutrophil chemotaxis, adhesion and mobilization, and superoxide production in addition to inhibition of NACHT-LRRPYD-containing protein 3 (NALP3) inflammasomes and interleukin (IL)1β processing and release.

3.1.3 Neutrophils

3.1.3a Inhibition of neutrophil chemotaxis: Colchicine concentrates intensively in leukocytes. *In vitro*, colchicine at concentrations as low as 0.1nM inhibits neutrophil chemotaxis and the release of a glycopeptide crystal-derived chemotactic factor (CCF) from neutrophil lysosomes after phagocytosis of monosodium urate crystals (MSU) [9]. A MSU-induced chemotactic factor S100A8/9 (thought to be the same molecule as CCF [10]) released from neutrophils was shown to substantially amplify neutrophil recruitment [11]. Recently, colchicine was shown to dampen inflammation via regulation of the myeloid inhibitory C-type lectin-like receptor (MICL), which is expressed by macrophages, monocytes, neutrophils, myeloid and plasmacytoid dendritic cells. Gagné et al demonstrated that colchicine inhibits the MSU-induced loss of cell surface MICL in neutrophils and subsequent IL8 production [12].

3.1.3b Neutrophil adhesion, mobilization and recruitment: Through microtubule depolymerisation, colchicine interferes with neutrophil adhesion and recruitment to inflamed tissue [13][14]. At nanoconcentrations (50% inhibitory concentration, IC_{50} of 3 nM) or typical doses used as prophylaxis, colchicine alters the distribution of E-selectin on endothelial cell surfaces and eliminates the adhesiveness for neutrophils. At higher microconcentrations (IC_{50} = 300 nM), colchicine induces shedding of neutrophil adhesion molecules (L-selectin) and prevents further neutrophil recruitment [14]. Colchicine was shown to inhibit neutrophil adhesion and mobility in crystal-induced neutrophil activation by selective inhibition of tyrosine phosphorylation [15]. A recent study has demonstrated that colchicine reduces crystal-induced tyrosine phosphorylation of Tec, which is likely the principle kinase in crystal induced neutrophil activation [16]. Paschke et al found that colchicine inhibits the deformability and motility of human neutrophils in confined spaces, which is crucial for neutrophil extravasation during inflammation [17].

3.1.3c Inhibition of superoxide production from neutrophil: Colchicine selectively suppresses MSU-induced superoxide production by neutrophils *in vitro*; this effect is mediated by inhibition of microtubules [15]. Recently, Chia et al demonstrated that

colchicine inhibits MSU-induced superoxide production by murine peritoneal macrophages *in vivo* at doses 100 times lower than that required to inhibit neutrophil infiltration [18]. This suggests that superoxide anion production is more sensitive to suppression by colchicine than microtubule formation involved in cell migration. Colchicine has been shown to reduce oxidative stress by reducing calcium (Ca^{2+}) influx into neutrophils [19].

3.1.4 Inhibition of NALP3 inflammasome and innate immune responses—MSU and calcium pyrophosphate dihydrate crystals (CPPD) were shown to specifically activate the NALP3 inflammasome, also known as the cryopyrin inflammasome. At high concentrations (5μM), colchicine suppresses MSU-induced NALP3 inflammasomes, responsible for caspase-1 activation and subsequent IL1β and IL18 processing and release [20]. The mechanism by which colchicine inhibits this NALP3 inflammasome activation is still unknown. It could possibly be related to the disruption of microtubule dependent transport of mitochondria to the endoplasmic reticulum. The assembly of NALP3 in the endoplasmic reticulum with its adaptor, Apoptosis associated Speck like protein containing Caspase recruitment domain (ASC), is required for the activation of inflammasomes [21] [22][23]. Suppression of MSU-induced NALP3 inflammasome activity occurs at doses much higher than those used therapeutically and thus this may not be the primary therapeutic action of colchicine responsible for aborting flares of acute crystal arthropathies [24][1]. However, the concentration of colchicine in neutrophils may be more than 16 times the peak concentration in plasma [25]. It may be possible for a continuous low prophylactic dose of colchicine to achieve a high enough intracellular concentration in macrophages to inhibit NALP3 inflammasome activation. Colchicine may increase the threshold for initiation of full-blown NALP3 inflammasome activation in part by diminishing (without eliminating) subclinical inflammation [26]. Prophylactic therapy with colchicine also regulates the innate inflammatory response by blocking intracellular signalling pathways by targeting nuclear factor kB (NF-kB) or caspase-1 [27].

The effects of colchicine on macrophages have received much attention (Figure 2). Colchicine was shown to modulate lipopolysaccharide-induced secretion of tumor necrosis factor (TNF)a by liver macrophages in a rat model [28]. In a mouse brain macrophage cell line, colchicine inhibited ATP-induced release of IL1β via preventing microtubule reorganization and inhibiting activation of the Ras homolog gene family, member A (RhoA)/Rho-associated, coiled-coil containing protein kinase (ROCK) pathway [29]. Marques-da-Silva *et al*. recently demonstrated that colchicine is a potent inhibitor of pore formation induced by activation of both purinergic receptors P2X7 and P2X2 both *in vitro* and *in vivo* [30]. In the presence of colchicine, peritoneal mouse macrophages showed less ATP-induced permeability to ethidium bromide, and less reactive oxygen species (ROS) formation, nitric oxide (NO) and IL1β release. After colchicine treatment, mice inoculated with lipopolysaccharide and ATP also had diminished ROS, IL1β, interferon-γ and NO production. The formation of P2X7 pores is a necessary step in the innate immune response for triggering ATP-induced NALP3 inflammasome activation [31]. This event is upstream to microtubule depolymerisation and may represent a new therapeutic target for treatment of chronic inflammation [32].

3.1.5 Stimulation of antigen presentation—At relatively low concentrations (3μg/ml), mice colchicine promotes maturation of dendritic cells, generation of cytokines and the presentation of antigen to allogenic naive CD4+ lymphocytes [33]. Highlighting the importance of microtubules in cells processing of antigens, this stimulatory effect of colchicine on dendritic cells (as antigen presenting cells) was further demonstrated in human dendritic cells [34][35][36].

3.1.6 Anti-fibrotic and cardiovascular protective effects—Colchicine has anti-fibrotic effects. In a rat model of cyclosporine nephrotoxicity, colchicine inhibited tubulointerstitial fibrosis by stimulating B-cell lymphoma 2 (Bcl-2) expression and suppression of caspase-3 and thereby suppressed renal cell apoptosis [37]. In a rat model of hypertensive chronic kidney disease, colchicine inhibited renal fibrosis via inhibition of RhoA signalling and infiltration of inflammatory cells [38]. In a rat model, colchicine inhibited liver fibrosis by inhibiting the activation of hepatic stellate cells and induced stellate cell apoptosis [39]. In an encapsulating peritoneal sclerosis model, colchicine inhibited anti-transforming growth factor (TGF)-β1 activity [40]. In an *in vitro* study using human lung fibroblasts, colchicine inhibited myofibroblast differentiation via Rho/ serum response factor (SRF) dependent, but Smad independent signalling [41]. The cardiovascular applications of colchicine have been evolving in the last decade. FMF patients treated with colchicine were observed to have lower markers for endothelial dysfunction and cardiovascular risk such as β-thromboglobulin and mean platelet volume [42] [43]. Colchicine inhibited intimal hyperplasia and leukocyte vascular endothelial growth factor (VEGF) expression in an angioplasty model in dogs [44]. In a rat pulmonary arterial hypertension model, colchicine suppressed smooth muscle cell proliferation, increased cell apoptosis and reduced protein expression of inflammation (TNF-a and NF-κB) [45]. Colchicine was shown to have synergistic protective effects with atorvastatin on endothelial function, reduced C-reactive protein (CRP) and lipoprotein associated phospholipase A2 (Lp-PLA2), and enhanced NO production in rats [46]. The clinical applications of colchicine in pericarditis and atherosclerosis have been under intense investigation.

3.2 Colchicine metabolism and toxicities

Colchicine has a narrow therapeutic window. When prescribed daily and chronically for FMF, the most common adverse reactions (up to 20%) are abdominal pain, diarrhoea, nausea, and vomiting. These effects are usually mild, transient, and reversible upon lowering the dose. Prescribed acutely for gout flares with doses up to 1.8 mg within 2 hours, the most common adverse reaction is diarrhoea (23%) and pharyngolaryngeal pain (3%) [47]. At therapeutic doses of colchicine, blood dyscrasias have been reported including myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia [48]. Colchicine is a substrate for intestinal and hepatic cytochrome P450 3A4 (CYP3A4), and also a substrate for P-glycoprotein 1 (P-gp) reflux transporter. Colchicine is primarily eliminated by hepatobiliary excretion. Renal excretion accounts for 10–20% of colchicine elimination in patients with normal renal function. Consistent with the current understanding of colchicine metabolism, certain drugs increase the potential for colchicine toxicity via modulation of P-gp and CYP3A4 activity. Cases of myopathy and/or rhabdomyolysis in patients receiving colchicine have been reported with concomitant use of

statins, fenofibrate/gemfibrozil, cyclosporine, or digoxin. Toxicity has also been reported in a patient who regularly (daily) consumed grapefruit juice while being treated chronically with colchicine. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine with concomitant P-gp inhibitors (eg cyclosporine, ranolazine) and strong CYP3A4 inhibitors (eg. clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone, and some protease inhibitors). In the majority of cases, the doses of colchicine were within the therapeutic range. An algorithm for dosage adjustments of colchicine during concomitant treatment with multiple CYP3A4/P-gp inhibitors to improve safety have been proposed based on an *in vivo* single dose pharmacokinetic study [49]. P-gp is encoded by the multidrug resistance gene-1 (MDR1, adenosine triphosphate-binding cassette transporter: ABCB1, P-glycoprotein) and is an ATP-dependent efflux pump that regulates the tissue distribution of colchicine. The P-gp/MDR1 gene is highly polymorphic with more than 70 single nucleotide polymorphisms (SNPs) defined to date [50]. Polymorphisms of the MDR1 gene have been shown to change both the expression level and function of P-gp, and might be associated with colchicine resistance in some small sample studies in FMF [51][52][53] and BD [54]; but not in all studies [55][56]. In general, further studies with a larger sample size are needed to better understand the role of MDR1 gene polymorphisms in the colchicine response of patients with different conditions.

Apart from avoidance of the use of colchicine with adversely interacting drugs, colchicine dose reductions should be considered in patients with renal or hepatic impairment, and the elderly. Some recommendations suggest reducing the colchicine dose by 50% in patients with creatinine clearance below 50 ml/minute [2]. The American College of Rheumatology guidelines recommended exercising caution and instituting colchicine dose adjustment in renal impairment at the discretion of the treating clinician [57].

3.3 Therapeutic uses of colchicine

The use of colchicine has been better established in gout and FMF. Beyond these, the possible therapeutic roles of colchicine in rheumatic osteoarthritis (OA), BD or non-rheumatic conditions, including pericarditis, artherosclerosis and liver cirrhosis are still ongoing and as described below, appear promising for some of these conditions.

3.3.1 Rheumatic diseases

3.3.1a Gout: Colchicine has been used ubiquitously in abortion of acute gouty attacks, yet there remain few large randomized controlled trials evaluating the optimal dosing frequency and dosage (Table 1). There has only been one recent randomized, double blinded, placebo controlled trial in 2010, the AGREE trial (Acute Gout Flare Receiving Colchicine Analysis) that has looked at high versus low doses of colchicine, i.e. 8 versus 3 tablets (0.6 mg) in 24 hours in early acute gout flares [47]. Superiority of colchicine was demonstrated over placebo in 185 patients randomized to high dose or low dose of colchicine or placebo with responder rates 32.7%, 37.6% and 15.5% respectively; there was no significant difference between the high and low dose groups. The high dose treatment arm had more associated gastrointestinal side effects. The general consensus for the treatment of acute gout is to use low doses of colchicine. In view of its potential side effects, including renal, hepatic and

gastrointestinal side effects, dosage adjustments also need to be considered. The European League against Rheumatism EULAR 2011consensus guidelines recommended low dose colchicine, up to 3 doses of 0.5mg in the first 24 hours for the treatment of gout [58]. The ACR guidelines also recommended colchicine as an appropriate primary treatment option in acute gout attacks, with a loading dose of 1.2 mg followed by 0.6mg [57].

The effectiveness of colchicine in prophylaxis of gout flares after the initiation of urate lowering therapy has been demonstrated [59][60]. The EULAR guidelines recommended prophylaxis for acute gout attacks in the first 6 to 12 months of therapy with urate-lowering agents [58].

3.3.1b Osteoarthritis: The association of uric acid and OA has long been observed [61] [62], and a pathological link between the two conditions has been proposed [63]. In a recent large study of human cadaveric ankles, MSU were strongly associated with cartilage lesions as well as immunohistochemical changes of cartilage degeneration and repair [64]. A study of human chondrocytes and cartilage explants also demonstrated the profound inhibitory effect of MSU on chondrocyte viability and function [65]. In a study among OA subjects without clinical gout, a strong positive association was identified between synovial fluid uric level and IL18, IL1β and OA severity as measured by imaging [66]. This suggested that monosodium uric acid may contribute both to the initiation and/or propagation of cartilage degradation in OA although it may do so in forms other than crystalline.

The pain and symptom relieving effects of colchicine for knee OA have already been demonstrated in three small RCTs (Table 1) [67][68][69]; In the first study of 39 knee OA subjects with clinical signs of inflammation, despite background piroxicam therapy, colchicine in addition to intraarticular steroid treatment produced significantly greater symptomatic improvement and reduction of signs of knee inflammation than intraarticular steroid and placebo [67]. The second study showed that despite background therapy with nimesulide, 36 subjects with knee OA had greater symptomatic improvement defined by acheiving a 30% reduction in Western Ontario and McMaster Universities Arthritis Index at 20 weeks with colchicine than placebo (57.9% versus 23.5%) [68]. Another study of 61 knee OA subjects demonstrated that colchicine added to usual treatment (analgesics, non steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy) led to greater improvement in patient and physician global assessment at the end of 3 months versus placebo [69]. A registered single center RCT (NCT02176460) with larger sample size has started, aiming to compare colchicine versus placebo in reducing pain and function, in addition to usual treatment in subjects with knee OA. It includes evaluation of serum and synovial fluid biomarkers in an attempt to delineate colchicine's underlying mechanisms of action and impact on joint tissue metabolism [70].

3.3.1c Behcet's disease: In Behcet's disease, colchicine is postulated to be useful for mucocutaneous involvement. A small open-label study of 14 subjects in Japan showed equivocal response in the frequency of ocular attacks between treatment with monotherapy with infliximab compared with combination therapy with colchicine ($p<0.05$) [71]. A multicentered randomized controlled trial in Iran involving 169 patients demonstrated significant improvement based on the Iran Behcet's Disease Dynamic Activity Measure

(IBDDAM) in the colchicine treatment arm compared with placebo (mean difference colchicine versus placebo, −0.80 versus 0.46, p = 0.00016) [72]. An open-label study in subjects with mucocutaneous BD revealed significant reduction in oral ulcers and serum inflammatory cytokines IL-6, IL-8 and TNFα with the combination of colchicine and levamisole [73].

3.2.1d Familial Mediterranean fever (FMF): Familial Mediterranean fever (FMF) is a rare inherited autosomal recessive autoinflammatory disorder caused by mutations of the FMF gene (MEFV, Mediterranean Fever) on chromosome 16p13.3, which encodes pyrin. It is characterized by recurrent and self-limited episodes of fever and painful serositis, related to neutrophil activation at serosal surfaces. It affects predominantly ethnic groups around the Mediterranean basin [74]. Colchicine represents the standard first line treatment for FMF and has to be continued for life. A good, partial response to colchicine was seen in 87% of the patients in reducing severity, duration and frequency of attacks [75][76][77]. Although colchicine does not totally prevent febrile attacks, its long term use can arrest the progression of AA amyloidosis. Consensus guidelines have been developed for the chronic use of colchicine in children with FMF. Compliance should be carefully monitored [77].

3.3.2 Non rheumatic diseases

3.3.2a Pericarditis: Exciting new developments have been made in recent years on the application of colchicine for treating acute, recurrent pericarditis, as well as post-pericardiotomy syndrome. This is especially relevant as there are no definitive therapies for the treatment of pericarditis. In an open-label randomized controlled trials, COlchicine for REcurrent pericarditis (CORE) [78] and COlchicine for acute PEricarditis (COPE) [79], colchicine given as an adjunct to conventional treatment, has demonstrated significant reduction in recurrence of pericarditis at 18 months. Subsequent larger multicenter RCTs, Colchicine for Recurrent Pericarditis (CORP) [80] and the CORP-2 trial [81], colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in subjects with multiple recurrences. In a multicenter RCT, colchicine was shown to reduce the risk of the first recurrent attack of pericarditis (relative risk reduction in the colchicine group, 0.56; 95% confidence interval, 0.27 to 0.73; number needed to treat 3) [82]. The efficacy and safety of colchicine for the primary prevention of the postpericardiotomy syndrome (PPS), postoperative effusions, and postoperative atrial fibrillation (POAF) has been shown in the COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial [83]. A larger multicenter COPPS2 trial evaluating the use of colchicine for the primary prevention of PPS, postoperative effusions, and POAF is currently in a recruitment phase (NCT00128453); potentially it may provide evidence to support the use of preoperative colchicine to prevent several postoperative complications [84]. Several meta-analyses support the use of colchicine in the treatment of pericarditis [85][86][87][88][89](Table 2). Colchicine compared to standard treatment with aspirin or NSAIDs was associated with comparable adverse effects and drug discontinuation rates. Gastrointestinal intolerance was the most frequent side effect (mean incidence 8%). Based on early observational trials, the European Society of Cardiology has recommended colchicine as a treatment option for pericarditis and post-pericardiotomy syndrome (level of evidence B, class IIa), either as an adjunct to NSAIDs or as monotherapy [90]. The evidence

regarding the clinical utility of colchicine in pericarditis is still evolving, in general it has a high potential for future clinical use.

3.3.2b Use of colchicine in atherosclerosis and cardiovascular diseases: A recent large randomized, double blinded study in Canada consisting of 532 subjects who had coronary artery disease and who took who took colchicine 0.5mg daily for a median of three years, demonstrated a reduction in the composite incidence of acute cardiovascular events, or non-hospital cardiac arrests or non-cardioembolic ischaemic strokes in the colchicine treatment arm (5.3% vs 16% $p<0.001$) [91]. Deftereos et al also demonstrated a significant reduction in bare metal stent stenosis of 196 patients post percutaneous coronary intervention who were randomized to either colchicine 0.5mg twice a day or placebo (16% versus 33%, $p<0.007$) [92]. In a RCT of 80 subjects with acute coronary or cerebrovascular event, low dose colchicine given at 0.5mg twice daily compared with placebo, did not show a significant difference in high sensitivity CRP levels or platelet function at 30 days [93]. In another RCT in 267 subjects with chronic heart failure, colchicine compared with placebo did not reduce the proportion of subjects achieving improvement in the New York Heart Association class or the composite acute coronary syndrome or stroke end points, although CRP and IL6 were significantly reduced in the colchicine group [94].

3.3.2c Hepatic Diseases: Colchicine has anti-fibrotic effect and possibly a modulatory role in bile composition. However, the results of clinical trials have been inconsistent. In a placebo-controlled multicenter study in 549 patients with advanced alcoholic cirrhosis [95], colchicine failed to reproduce the previously reported favorable effect on mortality [96]. A meta-analysis combining the results of 15 RCTs encompassing 1,714 subjects with alcoholic or non-alcoholic liver cirrhosis, demonstrated no significant effects of colchicine on mortality, liver related mortality, complications and other outcomes [97]. In a recent double blind, randomized controlled trial in 74 subjects with chronic liver cirrhosis and who could not be treated with alpha-interferon, Muntoni et al demonstrated that colchicine 1mg daily significantly increased survival (94.6% vs 78.4% $p=0.001$), and decreased serum N-terminal peptide of type III procollagen (a biomarker of liver fibrosis) over a follow up period of 4.4 years [98].This suggests there may be a beneficial effect of colchicine for selected subjects with liver cirrhosis. In an open-label study of 91 subjects with primary biliary cirrhosis who had an incomplete response to ursodeoxycholic acid, a regimen of 6 months of add-on colchicine followed by add-on methotrexate, demonstrated a significant decrease in liver enzymes and histological fibrosis and inflammation scores [99].

3.3.2d Other indications: Colchicine has been tested in a variety of dermatological conditions and has shown a certain degree of efficacy in recurrent aphthous stomatitis [100] [101] and chronic urticaria [102][103], but not in hidradenitis suppurativa [104] or peyronie's disease [105]. The benefits of colchicine were demonstrated in a small three-arm study comparing prednisolone alone versus prednisolone and cyclophosphamide versus prednisolone and colchicine in pulmonary fibrosis. There were significant improvements in dyspnoea in the prednisolone and colchicine group compared with the two other groups [106].

4. CONCLUSION

Colchicine has been the first line therapy for the treatment of acute gouty arthritis and FMF. Due to the anti-inflammatory and anti-fibrotic activities, the therapeutic use of colchicine has extended beyond arthritis. The exact mechanisms of action underlying its efficacy are not completely understood and remain under active investigation. Current results suggest that colchicine downregulates multiple inflammatory pathways and modulates innate immunity. As demonstrated by this review, there are many potential therapeutic uses for colchicine or its analogues.

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List of abbreviations

ABCB1	adenosine triphosphate-binding cassette transporter 1
ASC	Apoptosis associated Speck like protein containing Caspase recruitment domain
ATP	adenosine triphosphate
Bcl-2	B-cell lymphoma 2
BD	Behcet's disease
Ca^{2+}	calcium
Caspase	cysteine-dependent aspartate-directed proteases
CCF	crystal-derived chemotactic factor
CPPD	calcium pyrophosphate dihydrate crystals
CRP	C-reactive protein
CYP3A4	cytochrome P450 3A4
FMF	familial Mediterranean fever
IC_{50}	50% inhibitory concentration
IL	interleukin
MDR1	multidrug resistance gene-1
MLCK	myosin light chain kinase
MICL	myeloid inhibitory C-type lectin-like receptor
MSU	monosodium urate crystals
MyD88	myeloid differentiation primary response gene 88

NALP3	NACHT-LRRPYD-containing protein 3
NF-kB	nuclear factor kB
NO	nitric oxide
NSAIDs	non steroidal anti-inflammatory drugs
P-gp	P-glycoprotein 1
P2X2	P2X7, purinergic receptors P2X2, P2X7
ROS	reactive oxygen species
RhoA	Ras homolog gene family, member A
ROCK	Rho-associated, coiled-coil containing protein kinase
SNPs	single nucleotide polymorphisms
SRF	serum response factor
TLR	toll-like receptors
TGF-β1	transforming growth factor beta-1
TNFα	tumor necrosis factor α
VGEF	vascular endothelial growth factor

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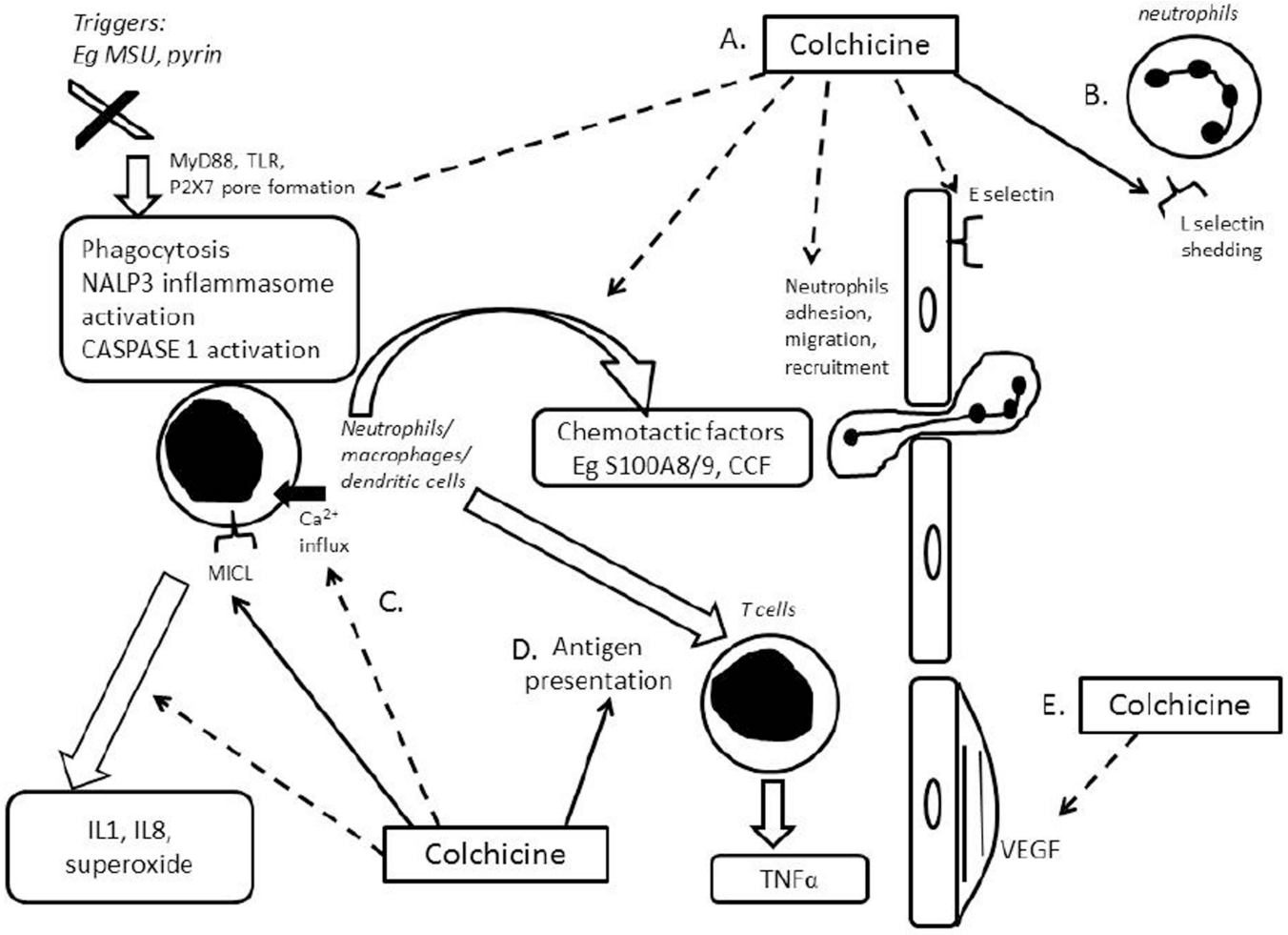

Figure 1. Summary of the main anti-inflammatory mechanisms of action of colchicines

Dashed lines refer to inhibitory activities and continuous lines to stimulatory activities of colchicine. The main mechanisms of action include the following: A. Colchicine inhibits activation of innate immunity, NALP3 inflammasome activation, CASPASE-1 activation; inhibits release of chemotactic factor release from neutrophils and then neutrophil recruitment; B. At low concentrations, colchicine inhibits expression of E-selectin on endothelial cells and prevents neutrophil adhesion. At high concentrations, colchicine promotes shedding of L-selectin from neutrophils and prevents further recruitment; C. Colchicine inhibits neutrophil activation and release of IL1, IL8, and superoxide; D. Colchicine promotes maturation of dendritic cells to act as antigen presenting cells; E. Colchicine inhibits vascular endothelial growth factor (VEGF) and endothelial proliferation. CASPASE= cysteine-dependent aspartate-directed proteases, CCF= crystal-derived chemotactic factor, MSU=monosodium urate (gout) crystals, MICL= myeloid inhibitory C-type lectin-like receptor, NALP3=NACHT-LRRPYD-containing protein 3, TLR=toll-like receptors, MyD88= myeloid differentiation primary response gene 88, VEGF= vascular endothelial growth factor.

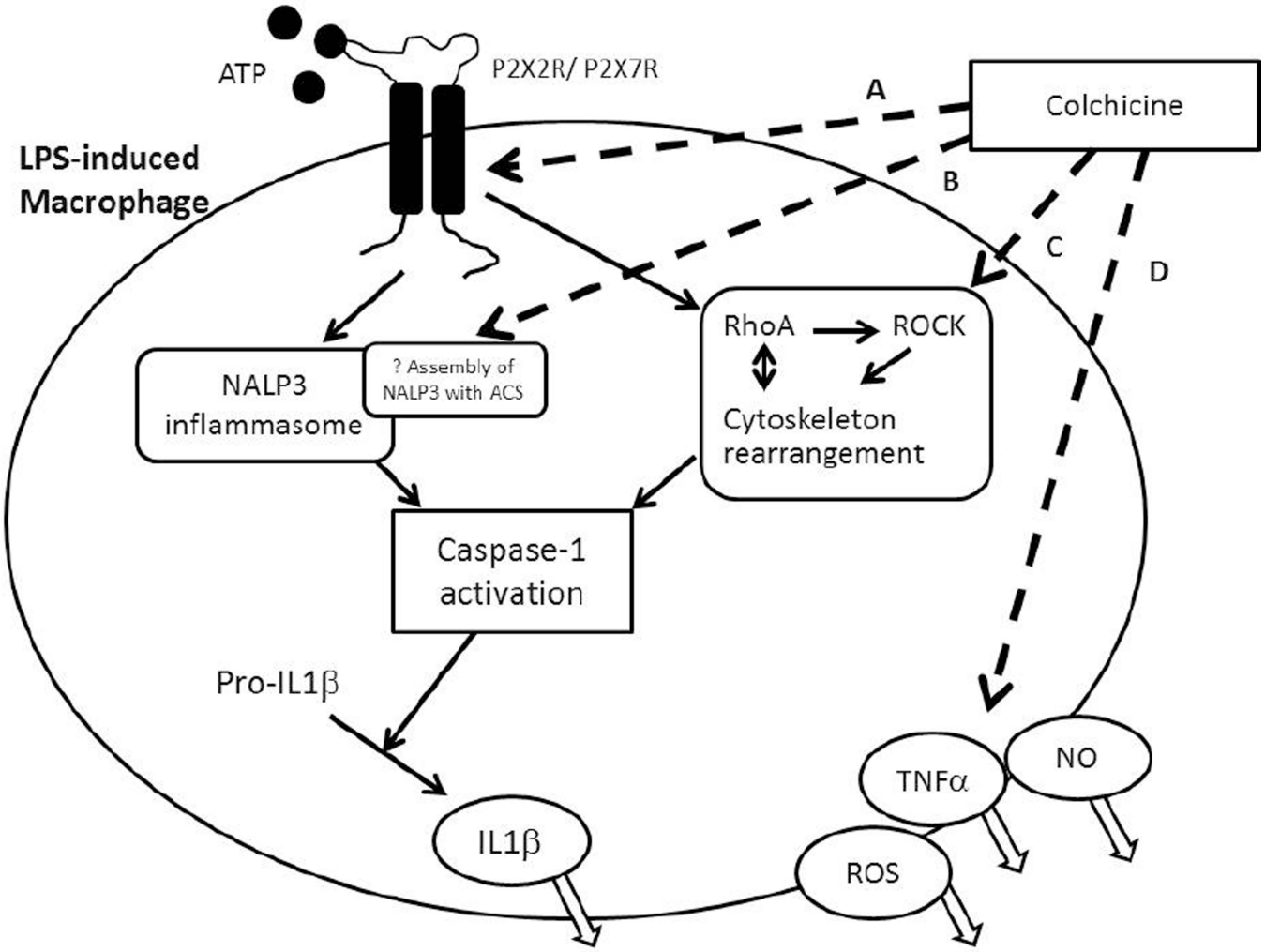

Figure 2. Summary of the effects of colchicine on macrophages

Dashed lines refer to inhibitory activities and continuous lines to stimulatory activities of colchicine. A. Colchicine inhibits activation of P2X2 and P2X7 receptors and blocks cationic dye uptake (via recruitment of the pannexin-1 membrane pore) and further pro-inflammatory cascades without affecting cell death. B. Colchicine inhibits the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome, possibly via inhibition of assembly of NALP3 with Apoptosis associated Speck like protein containing Caspase recruitment domain (ACS); C. Colchicine inhibits the RhoA/ Rho effector kinase (ROCK) pathway via cytoskeleton rearrangement and thus the activation of caspase- 1 and downstream maturation and release of IL1β; D. Colchicine inhibits release of various substances including reactive oxygen (ROS), nitrite oxide (NO) and tumor necrosis factor (TNF)α. Caspase-1= cysteine-dependent aspartate-directed proteases-1, IL= interleukin, LPS= lipopolysaccharide, P2X2 and P2X7= purinergic receptors.

Table 1

Summary of the uses of colchicine in arthritis.

Author Country Year	**Disease group**	**Study Design**	**subject**	**n**	**Intervention**	**FU**	**Outcome**
Terkeltaub, et al USA, 2010 [47]	Gouty arthritis	RCT, DB	Acute gouty arthritis	184	low-dose colchicine −(1.8 mg total over 1h) vs. high-dose colchicine −(4.8 mg total over 6h) vs. placebo	24h	*Positive* • Responder rates high vs. low dose colchicine vs. placebo: (32.7% vs. 37.6% vs. 15.5%) • No significant difference between the high and low dose colchicine groups. • High dose colchicine group had more gastrointestinal side effects
Das, et al India 2002 [67]	Knee OA	RCT, DB	Knee OA with inflammation - despite NSAIDs - All had IA steroid	39	Colchicine 0.5mg bid vs. Placebo	20 w	*Positive* Higher proportion in colchicine group achieved 30% improvement - index knee VAS-pain (69% vs. 15%) - KGMC scores (74% vs. 45%)
Das, et al India 2002 [68]	Knee OA	RCT, DB	Primary knee OA Addition of NSAID	36	Colchicine 0.5mg bid vs. placebo	20 w	*Positive* Higher proportion in colchicine group achieved 30%
							improvement • index knee VAS-pain (52.6% versus 17.6%) • WOMAC (57.9% vs. 23.5%)
Aran, et al Iran 2011 [69]	Knee OA	RCT, DB	primary knee OA Women, Postmenopausal	61	Colchicine 0.5mg bid vs. placebo	16 w	*Positive* *In colchicine group:* • Less paracetamol consumption • Better patient global assessment (11.14+/−4.0 6 vs. 3.14 +/−2.18) • Better physician global assessment (9.83 +/− 3.8 vs. 3.72+/−3.35)
Leung, et al Singapore NCT02176460 [70]	Knee OA	RCT, DB	Primary knee OA	120	Colchicine 0.5mg bid vs. placebo	16 w	*In recruitment phase*

n=sample size; OA= osteoarthritis; RCT = randomized controlled trial; DB = double blinded; SC = single center; NSAIDs = non-steroidal anti-inflammatory drugs; IA = intra-articular; vs. = versus; bid = twice daily; h= hour; d = day; w = week; VAS = visual analogue scale; KGMC = total King George's Medical College (KGMC) scale; WOMAC= total Western Ontario and McMaster University Osteoarthritis scores.

Table 2

Summary of studies on the adjunctive use of colchicine in pericarditis.

Author	Year	design	setting	n	FU	Trial Name	Subject character	Treatment	Primary Outcome	*Results*
Imazio et al [78]	2005	RCT, OL	SC	84	6 m	CORE	Recurrent pericarditis	colchicine (1.0–2.0 mg D1, maintenance 0.5–1.0 mg/d	Recurrent pericarditis at 18m; symptom persistence at 72 h	*Positive* Recurrent rates at 18 months −(24.0% colchicine vs 50.6% placebo; p = .02; NNT = 4.0) Symptom persistence at 72h −(10% colchicine vs 31% placebo; p = 0.03).
Imazio et al [80]	2011	RCT, DB	MC	120	6 m	CORP	Recurrent pericarditis	Colchicine 1–2mg D1, maintenance 0.5–1mg/d	2nd recurrence of pericarditis	*Positive* 24% colchicine vs. 55% placebo; p <0.05
Imazio et al [81]	2014	RCT, DB	MC	240	6 m	CORP 2	Recurrent pericarditis	Colchicine 1–2mg D1, maintenance 0.5 mg/d	Subsequent recurrence (>2nd)	*Positive* 21.6% colchicine vs 51% placebo, p=0.009
Imazio et al [79]	2005	RCT, OL	SC	120	3 m	COPE	Acute pericarditis	colchicine (1.0–2.0 mg D1, maintenance 0.5–1.0 mg/d	Recurrent pericarditis at 18m; symptom persistence at 72 h	*Positive* Recurrent rates at 18 months −(10.7% colchicine vs. 32.3% placebo; p=0.004; NNT=5) Symptom persistence at 72h −(11.7% colchicine vs. 36.7% placebo; p=0.003).
Imazio et al [82]	2013	RCT, DB	MC	240	3 m	ICAP	Acute pericarditis	Colchicine 0.5 mg bid (for BW >70 kg) Colchicine 0.5 mg/d (for BW ≤70 kg)	1st recurrence of acute pericarditis	*Positive* 16.7% colchicine vs 37.5% placebo, p<0.001 RRR 0.56; CI 0.30 to 0.72; NNT 4.0; p<0.001
Imazio et al [83]	2010	RCT, DB	MC	360	1 m	COPP S	PPS	POD3: 1mg bd, maintenance 0.5mg bd	Incidence of PPS	*Positive* 8.9% colchicin e vs 21.1% placebo, p<0.002
Imazio et al [84]	2013	RCT, DB	MC	360	1 m	COPP S2	PPS	POD3: 1mg bd, maintenance 0.5mg bd	Incidence of PPS, Postopera tive effusions, POAF	*in recruitment phase*

Meta Analyses

Author	Yea r	Number of Trials	Setting	*Results*	
Kuo et al [85]	2009	3	Primary and secondary prophylaxis of pericarditis	*Positive*	AR 21.6% NNT 5
Imazio et al [86]	2012	5	Pericarditis prevention	*Positive*	RR 0.40 CI 0.30–0.54

Author	Year	design	setting	n	FU	Trial Name	Subject character	Treatment	Primary Outcome	*Results*
Lotrionte et al [88]		2013	7		Acute or recurrent pericarditis			*Positive*	Reduced risk of treatment failure (OR 0.23 CI 0.11–0.49) recurrent pericarditis (OR 0.39 CI 0.20–0.77)	
Imazio et al [87]		2011	4		Primary prevention of PPs			*Positive*	OR 0.38 CI 0.22–0.6	
Alam et al [89]		2012	5		Recurrent pericarditis or primary Prevention of PPs			*Positive*	Overall (RRR 20.3%, NNT 4.9) Recurrent Pericarditis (RRR 33.3% and NNT 3.0). Primary prevention of PPS (RRR 12.1, NNT 8.3)	

n = sample size; FU= Follow Up duration; RCT: randomized control trial, SC = single centre; MC = multi centre; OL = open-label; DB = double blinded; y = year; m = month; d=day; POD =: Post-operation day, PPS = post pericardiotomy syndrome; POAF Post-operative Atrial Fibrillation;, P = Placebo; vs. = versus; OR = odd ratio; RR = relative risk; AR = absolute risk ratio; RRR = relative risk reduction; CI = 95% confident interval; NNT = number needed to treat; CORE = Colchicine for Recurrent Pericarditis; CORP =Colchicine for Acute Pericarditis; ICAP= Investigation on Colchicine for Acute Pericarditis; COPPS= Colchicine for Prevention of the PPS and POAF;