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# Colchicine in Renal Medicine: New Virtues of an Ancient Friend

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**Key Words**
Colchicine · Fibrosis · Kidney disease · Inflammation

**Abstract**
Colchicine is a plant-derived alkaloid that disrupts the cell microtubule system and accumulates in neutrophils, inhibiting neutrophil adhesion and recruitment. Colchicine has been used extensively in the prevention and treatment of gouty arthritis attacks, familial Mediterranean fever attacks and resultant AA amyloidosis, and recurrent pericarditis. Colchicine also disrupts the intracellular traffic of additional inflammatory and fibrosis mediators. Renal fibrosis is the final common pathway of chronic renal disease. Colchicine had anti-fibrotic effects in experimental diabetic nephropathy, renal mass reduction, and cyclosporine nephrotoxicity among others and is undergoing clinical trials for non-diabetic metabolic syndrome and diabetic nephropathy. In this review, we summarize the anti-inflammatory and anti-fibrotic properties of colchicine in experimental and clinical studies in renal diseases or other fibrotic disease processes with renal consequences. We also discuss the potential future uses of colchicine in renal medicine and challenges faced with its use in patients with impaired kidney function.



## Introduction

Colchicine is a plant-derived (colchicum autumnale) alkaloid that has been used for thousands of years to treat nonspecific arthritis [1]. Extensive clinical experience found colchicine safe and efficacious in treating gout and familial Mediterranean fever (FMF). Colchicine has additionally been used in the treatment of Behcet's disease, recurrent pericarditis, and some fibrotic disorders and is undergoing clinical trials for ischemic heart disease and arrhythmia [2]. The most recent area where colchicine has been used is in the field of cardiovascular disease. A recent meta-analysis demonstrated that in different populations of patients with established cardiovascular disease, colchicine reduced the composite cardiovascular outcome by almost 60% and showed a trend toward lower all-cause mortality in patients with coronary artery disease, acute coronary syndrome or stroke, post-angioplasty, or congestive heart failure [3].

Colchicine interferes with microtubule polymerization, thus interfering with the neutrophil function and having an anti-inflammatory effect [4]. In addition, colchicine has anti-fibrotic properties via a number of distinct mechanisms [5]. Since fibrosis is a ubiquitous final pathway in various kidney diseases, it is not surprising

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that experimental studies have shown favorable effects of colchicine in reducing fibrosis and in delaying the progression of kidney disease. Despite available and promising experimental evidence, scant clinical data regarding colchicine use in renal disease are available.

In this review, we discuss the mechanisms of the antifibrotic effect of colchicine in the context of renal disease. We summarize clinical and experimental data regarding colchicine efficacy and safety in renal diseases or in disease processes that may cause kidney injury. We also discuss the potential sources of underutilization as well as some putative indications in which colchicine may be effective.

## Mechanism of Action and Pharmacokinetics

Alpha and β-tubulin heterodimers constitute microtubules that elongate and contract, thereby altering the structure and function of the cytoskeleton [4]. Microtubules play a role in cell division as well as in many other physiologic processes including signal transduction, cell migration, and secretion [6]. The main mechanism of the action of colchicine is disruption of this microtubule system by binding to tubulins and blocking the assembly and polymerization of microtubules. Low concentrations arrest microtubule growth, whereas higher concentrations promote microtubule depolymerization [4]. Colchicine concentrates avidly in leukocytes, interfering with neutrophil adhesion, recruitment, and activation via microtubule depolymerization [7, 8]. Thus, colchicine decreases the release of superoxide anion from activated neutrophils and tyrosine phosphorylation in proteins involved in neutrophil responses to monosodium urate (MSU) and calcium pyrophosphate dehydrate crystals [9]. Not much data is available on colchicine actions on other immune functions. A detailed discussion of the anti-inflammatory effects of colchicine is beyond the scope of this paper and the reader is referred to reviews elsewhere [2, 6]. As examples, colchicine suppresses MSU crystal-induced NALP3 (NLRP3) inflammasome activation through the disruption of the intracellular localization of NALP3, thus preventing caspase 1 activation and release of interleukin (IL)-1β and IL-18 [10], downregulates lipopolysaccharide-induced tumor necrosis factor-alpha (TNF-α) secretion by liver macrophages [11] and prevents MSU-induced downregulation of the anti-inflammatory neutrophil receptor myeloid inhibitory C-type lectin-like receptor, thus attenuating inflammation [12].

After oral administration, colchicine is readily absorbed in the jejunum and ileum. Because of its lipophilic structure, it rapidly enters multiple cell types. It is metabolized by the intestinal and hepatic cytochrome P450 (CYP3A4) enzyme systems. Colchicine is a substrate for P-glycoprotein 1 (multidrug resistance protein 1) efflux pump and is predominantly eliminated by hepatobiliary excretion, with gastrointestinal tract lining cell turnover playing a role in its elimination through P-glycoprotein-1. Renal excretion accounts only for 10–20% of total colchicine elimination in patients with normal renal function [13].

## Colchicine in Renal Fibrosis

Fibrosis is a final common phenomenon in chronic nephropathies, irrespective of their etiology, and is characterized by glomerulosclerosis and/or tubulointerstitial fibrosis [14]. The process is active and much more complex than once thought. The key feature is the accumulation of fibroblasts and extracellular matrix (ECM). Fibroblasts are activated into myofibroblasts via a variety of mechanical factors and fibrogenic cytokines, such as transforming growth factor (TGF)-β1 [15, 16]. Therefore, it is plausible to think that preventing or ameliorating fibrosis may halt the progression of chronic kidney disease (CKD).

Colchicine has been used in a number of fibrogenic disease processes, particularly in hepatic fibrosis. The effects of colchicine on histological grade of hepatic fibrosis were explored in a limited number of studies. In a multicenter randomized placebo-controlled trial of patients with primary biliary cirrhosis, colchicine reduced the histological grading score when added to ursodeoxycolic acid [17]. However, a meta-analysis of randomized controlled studies did not reveal an overall remarkable benefit of colchicine in primary biliary cirrhosis [18]. As for the kidney, beneficial effects of colchicine have been observed in a number of primary fibrotic conditions of the kidney as well as in fibrotic processes in which the kidney is involved secondarily (Table 1).

Colchicine may curb fibrosis through anti-inflammatory and direct anti-fibrotic actions (Fig. 1).

Lymphocytes and macrophages contribute to renal fibrosis [19, 20]. Colchicine inhibits lymphocyte proliferation and function [21, 22]. In the rat chronic cyclosporine (CsA) nephrotoxicity model, colchicine prevented macrophage influx and renal tubulointerstitial fibrosis [23]. Similarly, colchicine prevented macrophage infil-

**Table 1.** Experimental and clinical studies of colchicine in the renal disease processes with prominent fibrosis or in fibrotic disorders in which kidney is involved collaterally

| Reference | Study design and setting | Outcome measures | Effects of colchicine |
|---|---|---|---|
| *Peritoneal fibrosis* | | | |
| Sagiroglu et al. [103] | Comparison of colchicine and sirolimus on peritoneal fibrosis induced by hypertonic peritoneal dialysis solutions in rats | Serum VEGF, TGF-β, and TNF-α levels. Peritoneal tissue histopathology | Fibrosis developed in all colchicine-treated rats, VEGF, TGF-β, and TNF-α values not different between colchicine and control groups. |
| Bozkurt et al. [104] | Antifibrotic and anti-inflammatory effects of colchicine in EPS in rats | Dialysate-to-plasma ratio of urea (D/P urea), dialysate WBC count, ultrafiltration volume, and morphological changes of parietal peritoneum | Colchicine increased UF volume, and decreased peritoneal cell count, peritoneal thickness, and neovascularization |
| Sayarlioglu et al. [105] | Effect of colchicine on peritoneal alterations induced by hypertonic PD solution in rats | The levels of TGF-β, TNF-α, and albumin in the peritoneal dialysate and blood, the levels of MDA in peritoneal dialysate. Histologic evaluation of peritoneal membrane | TGF-β and peritoneal thickness did not improve in colchicine-treated rats |
| *Nephrogenic systemic fibrosis* | | | |
| Chen et al. [106] | 1 patient with nephrogenic systemic fibrosis treated with colchicine | Skin response to treatment | Skin condition had significantly improved with colchicine treatment |
| *Retroperitoneal fibrosis* | | | |
| de Socio et al. [107] | 4 patients | Clinical and radiological improvement | Colchicine-induced complete or significant remission and prevented disease recurrence |
| Vega et al. [108] | 7 patients | Symptomatic and clinical improvement, time to normalization of inflammatory parameters, radiological changes | Within 3 months of colchicine, all patients had symptomatic improvement and 67% had clinical improvement. No recurrence or treatment failure was observed |
| *Cyclosporine nephrotoxicity* | | | |
| Sabry et al. [66] | Omega-3 fatty acids vs. colchicine on CsA nephrotoxicity in rats | Serum creatinine and kidney histopathology | Significantly lower morphological changes (tubular atrophy and interstitial fibrosis in inner medulla and inner strip of the outer medulla) in colchicine rats |
| Disel et al. [65] | Colchicine on CsA nephrotoxicity in rats | Renal function, serum malonyldialdehyde levels, apoptosis, TGF-β, kidney histopathology | Colchicine prevented the increase in MDA serum levels, TGF-β expression, and kidney apoptosis |
| Li et al. [23] | Colchicine on CsA nephrotoxicity in rats | Renal function and histopathology | Colchicine reversed the increase in serum creatinine, tubulointerstitial fibrosis, and upregulation of osteopontin |
| Li et al. [109] | Colchicine on CsA nephrotoxicity in rats | Kidney function and histopathology, protein levels, and caspase-3 enzymatic activity | Colchicine reversed decline in creatinine clearance rate, decreased tubulointerstitial fibrosis, apoptotic cells, caspase-3 activity |

**Table 1.** (continued)

| Reference | Study design and setting | Outcome measures | Effects of colchicine |
|---|---|---|---|
| Sobh et al. [110] | Colchicine on CsA nephrotoxicity in rats nephrotoxicity | Kidney function and histopathology | Colchicine prevented focal tubular atrophy and interstitial fibrosis |
| *Other forms of renal interstitial fibrosis* | | | |
| Zhang et al. [111] | Colchicine on progression of renal fibrosis in subtotal nephrectomy in rats | Systolic blood pressure, proteinuria, serum creatinine. Kidney histopathology | Colchicine has little impact on progression of CKD and associated histological changes |
| Ozdemir et al. [40] | Colchicine on interstitial fibrosis in renal allografts of recipients with FMF | Amyloid recurrence, interstitial fibrosis in allograft biopsies in the first, second, and third years after transplantation | Colchicine significantly reduced interstitial fibrosis at all time points. |
| McClurkin et al. [112] | Colchicine in rabbit anti-GBM disease | Renal function and histopathologic changes in the kidney | Colchicine significantly reduced the rise in serum creatinine and interstitial fibrosis |

FMF, familial Mediterrinean fever; CsA, cyclosporine; GBM, glomerular-basal membrane; MDA, malondialdehyde; VEGF, vascular endothelial growth factor; WBC, white blood cell; TGF-β, transforming growth factor; TNF, tumor necrosis factor; CKD, chronic kidney disease; UF, ultrafiltration.

tration and ECM deposition in rat diabetic nephropathy [24].

High TGF-β expression is a hallmark of and a key contributor to renal fibrosis [25–27]. Colchicine suppressed TGF-β1 mRNA expression, TGF-β1 secretion, and collagen synthesis, processing and release in cultured renal fibroblasts [28–30]. Colchicine also inhibited the release of fibronectin and fibroblast proliferation, and stimulated tissue collagenase activity [29, 31, 32].

Matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) degrade ECM proteins. Colchicine alters the expression of various MMPs and TIMPs including MMP-I and TIMPs [29, 33].

Epithelial-mesenchymal transition (EMT) has been implicated in renal fibrogenesis [34]. Epithelial cells undergo a morphologic change characterized by the loss of apico-basal polarity and epithelial intercelluler contacts, with increased motility and contractility [14]. In endothelial to mesenchymal transition, endothelial cells acquire fibroblastic properties and may contribute to the accumulation of activated fibroblasts and myofibroblasts in areas of kidney fibrosis [5, 35, 36]. Colchicine modulates epithelial cell migration [37, 38], ECM synthesis, and fibroblast functions [39]. The precise targets of colchicine in EMT remain to be elucidated.

Ozdemir et al. [40] extended these observations to human subjects. In a case–control study of 25 renal transplant recipients with amyloidosis secondary to FMF, allograft biopsies were performed during the first, second, and third years post-transplant. Colchicine use was associated with milder interstitial fibrosis in renal allografts of amyloidotic patients compared with nonamyloidotic controls who did not receive colchicine.

## Colchicine in Diabetic Nephropathy

Globally diabetes mellitus is the most common cause of CKD [41] and is characterized by kidney inflammation and ECM accumulation [42]. Functional preclinical studies and early clinical trials suggest that inflammation and macrophage infiltration are key drivers of DN progression [43, 44]. Thus, the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) is increased in DN [45, 46]. Indeed, ICAM-1 deficiency protected mice from DN, reducing macrophage infiltration, glomerular TGF-β1, and fibrosis [47, 48]. The renal monocyte chemoattractant protein-1 (MCP-1; CCL2) is also involved in the migration of the macrophage into the diabetic kidney [49].

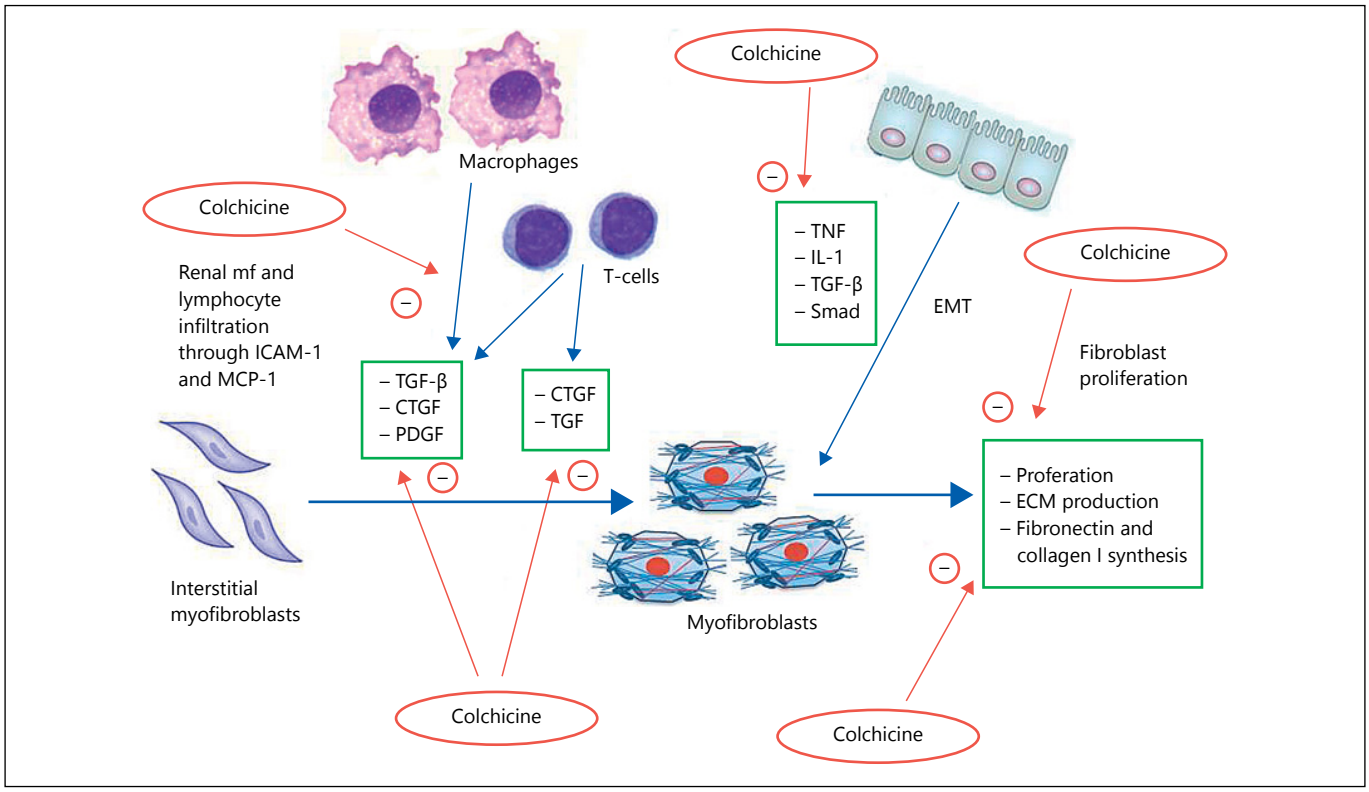


**Fig. 1.** Schematic illustration of anti-fibrotic effects of colchicine. Colchicine inhibits the secretion of TGF-β, connective tissue growth factor, and PDGF from leukocytes. These cytokines play a role in the transformation of resting fibroblasts to myofibroblasts, which are capable of secreting copious amounts of ECM. Colchicine also decreases myofibroblast proliferation and ECM synthesis and prevents the release or cell surface expression of inflammatory mediators such as ICAM-1, TNF-α, and IL-1β. CTGF, connective tissue growth factor; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; ICAM-1, intercellular adhesion molecule; MCP-1, monocyte chemoattractant protein; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor; TNF-α, tumor necrosis factor.

Colchicine reduced albuminuria, kidney MCP-1 and ICAM-1 expression, inflammatory cell infiltration (mainly monocytes and macrophages), and ECM accumulation in type 1 rat DN [24]. Furthermore, colchicine prevented the diabetes-induced podocyte depletion in rats [24]. This observation is of paramount importance, since podocyte depletion is a central phenomenon in CKD progression. However, human data are needed to confirm whether colchicine improves histopathologic changes. In this regard, an ongoing clinical trial (NCT02035891) is exploring whether low-dose (0.5 mg/day) colchicine reduces microalbuminuria within 18–36 months when compared with placebo in patients with type 2 diabetes and microalbuminuria who have been receiving stable treatment of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker for at least 3 months. The estimated primary completion date is of June 2018.

Neutrophil dysfunction in diabetic patients contributes to their increased susceptibility to infections and may contribute to systemic inflammation and DN, especially in patients with concomitant CKD. Spontaneous adherence and hydrogen peroxide synthesis of neutrophilic polymorphonuclear leukocytes are significantly higher in neutrophils from diabetic patients with overt proteinuria than from normoalbuminuric diabetic patients or from healthy controls [50, 51]. Neutrophils are activated in type-1 diabetes mellitus [52]. Leukocyte activation markers, CD11B on monocytes, and CD11B and CD66B on neutrophils, were higher in diabetic patients than in controls [53]. Neutrophils from type 2 diabetic patients release higher amounts of inflammatory cytokines under spontaneous and LPS-stimulated conditions, than non-diabetics [54]. In fact, neutrophils were more responsive to diabetic conditions than monocytes [54]. Taken together, neutrophil overactivity may contribute to tissue

injury and DN, especially when end-organ damage becomes apparent. Thus, colchicine, by decreasing neutrophil pro-inflammatory responses has the potential to ameliorate detrimental effects of activated neutrophils in diabetic subjects.

### Colchicine in Renal Mass Reduction

Renal mass reduction favors the progressive loss of renal function. In a rat remnant kidney model, colchicine inhibited glomerular RhoA activation and attenuated interstitial fibrosis and glomerular sclerosis independently of systemic blood pressure. Colchicine also reduced the pro-fibrotic cytokines TGF-β activity and connective tissue growth factor and the upregulation of ECM proteins, collagen I, and fibronectin. Besides this, colchicine decreased the renal infiltration of lymphocytes and macrophages [55]. RhoA/Rho-kinase signaling is dependent on an intact microtubule network [56] and RhoA kinase inhibition by colchicine could underlie the nephroprotective effect in renal mass reduction [57].

### Immunomodulatory Effects of Colchicine in Renal Transplantation

During the 1990s, experimental studies showed potent immunomodulatory actions and beneficial effects of colchicine in renal transplantation. However, despite promising initial results, clinical studies did not follow, possibly due to the advent of newer potent immunosuppressive drugs and reluctance to use colchicine with concerns of systemic toxicity.

Ostermann et al. [21] first showed that colchicine prevented allograft rejection in rats. Colchicine 40 μg/kg intraperitoneally starting 2 h prior to transplantation and continuing at 40 or 10 μg/kg/day resulted in the long-term survival of the allograft compared with controls. Chronic administration of colchicine led to systemic unresponsiveness as evaluated by T cells functional status in a mixed lymphocyte response (MLR) assay. Colchicine inhibition of MLR was dose-dependent [58]. Colchicine also inhibited the generation of cytotoxic T lymphocytes and the cytotoxic T-cell effector function in vitro and decreased the mononuclear cell infiltrates, IgM, C3, and fibrin deposition and the upregulation of activation markers, including IL-2 receptor, MHC class II, and ICAM-I in grafts, suggesting the selective inhibition of Th1 and the sparing of Th2 function. Colchicine also downregulated L-selectin in a dose-dependent manner and inhibited lymphocyte function in vitro [22]. In addition, colchicine prevented the interferon-gamma-induced expression of class II MHC molecules on the surface of colon cancer cells in culture [59]. The early phase of the immune response requires the expression of class II MHC molecules on the surface of antigen-presenting cells. Other contributory mechanisms include the decrease of TNF-α [60] and blockage of IL-2R expression on the surface of peripheral blood mononuclear cells [61]. Thus, colchicine downregulates the alloimmune response in vitro and prevents acute rejection and prolongs graft survival by blocking microtubule-dependent traffic of molecules to the cell surface of T cells and endothelial cells.

Research on colchicine in transplantation did not proceed to human studies. However, chronic allograft nephropathy (CAN) remains a major limitation of modern transplantation medicine [62]. Immunosuppressive drugs, particularly calcineurin inhibitors, contribute to CAN. Thus, the use of additional immunomodulatory drugs such as colchicine may help reduce the dose of calcineurin inhibitors to prevent both rejection episodes and CAN. In addition, colchicine may also be beneficial in CAN through its anti-fibrotic and anti-inflammatory actions [62]. A careful analysis of FMF kidney graft recipients currently on colchicine may provide further insights in this regard.

### Colchicine and Cyclosporine Nephrotoxicity

Calcineurin inhibitors constitute the backbone of modern immunosuppressive regimens for kidney transplantation [63]. However, the protracted use of calcineurin inhibitors may promote chronic graft dysfunction [64]. Colchicine improved experimental CsA nephrotoxicity, decreasing malonyldialdehyde serum levels, TGF-β expression, renal cell apoptosis, tubular atrophy, and interstitial fibrosis [65, 66].

### Colchicine for Preventing and Treating Renal Amyloidosis

Renal amyloidosis is a cause of end-stage renal disease [67, 68]. Over 20 structurally different proteins are known to cause amyloidosis [69]. However, 2 major forms are most related to kidney disease, namely, AL and AA amyloidoses.

### Primary (AL) Amyloidosis

The fibrils in AL amyloidosis consist of the fragments of the variable portion of monoclonal light chains [70]. Current therapy involves chemotherapy aimed at eliminating the plasma cell clone. High-dose intravenous melphalan followed by autologous stem cell transplantation has emerged as the most effective scheme [71]. In the 1980s and 1990s, colchicine was explored as a single therapy or as an add-on to chemotherapeutic regimens [72–76]. However, addition of colchicine did not provide a significant survival advantage over melphalan and prednisolone alone: in 220 patients with biopsy-proved AL amyloidosis, median survival was 8.5 months for colchicine, 18 months for melphalan and prednisone, and 17 months for melphalan, prednisone, and colchicine.

### Secondary Systemic (AA) Amyloidosis

AA amyloidosis is a disorder characterized by the abnormal systemic deposition of an acute phase reactant, serum amyloid A, in chronic inflammatory diseases. It usually results from FMF and some rheumatologic diseases or chronic infections [77]. Colchicine is used to prevent AA amyloidosis in patients with FMF. When started early and used at sufficient doses with a good compliance, development of AA amyloidosis can effectively be prevented in these patients [78]. Established AA renal amyloidosis is much less responsive to colchicine treatment [79].

The presence of AA amyloidosis does not preclude renal transplantation, but disease recurrence may lead to allograft loss if left untreated. Colchicine has been used effectively to prevent recurrent allograft dysfunction in amyloidotic patients with FMF who underwent renal transplantation. A retrospective study by Livneh et al. [80] revealed that colchicine treatment with a dose of at least 1.5 mg/day effectively prevented recurrent amyloidosis in the allograft kidney. Subsequent retrospective studies confirmed [81–83] that in patients maintained on adequate colchicine treatment, renal outcomes of amyloidotic patients were not different from those without amyloidosis. Unverdi et al. [84] reported that the beneficial effect of colchicine therapy was not evident in patients with AA amyloidosis secondary to rheumatologic diseases.

## Potential Uses of Colchicine in Renal Medicine

Although tested in a limited number of nephropathies, the anti-inflammatory, anti-fibrotic, and anti-proliferative properties of colchicine suggest that it may protect the kidney in additional disorders, including autosomal dominant polycystic kidney disease (ADPKD) and focal and segmental glomerulosclerosis (FSGS).

Previously we hypothesized that colchicine may be useful in ADPKD [85]. A number of factors have been implicated in the pathophysiology of ADPKD: increased apoptosis, unopposed proliferation of tubule cells, impaired polarization and planar cell polarity, impaired cAMP pathway, ciliary dysfunction, activated mammalian target of rapamycin pathway, and increased TNF-α production [85]. By limiting the proliferation of cyst-lining cells and inflammatory and fibrotic responses, colchicine may improve outcomes in ADPKD and should certainly be tested in experimental animal models.

FSGS is characterized by glomerular fibrosis and loss of podocytes and inflammation contributes to the process [86]. Preservation of podocytes [24] and the anti-inflammatory and anti-fibrotic actions of colchicine may limit the progression of FSGS. To our surprise, no studies have explored colchicine in FSGS yet.

## Concerns with Colchicine Use in Patients with Renal Function Impairment

There is a general reluctance to use colchicine even in conditions with relatively established indications. This reluctance may be multifactorial in origin. One reason is the lack of sufficient human data except for the data that are available on the prevention of renal AA amyloidosis. Furthermore, there is no randomized controlled study conducted in other nephropathies. Another, perhaps more important, reason for the underutilization of colchicine is the concern due to drug-related toxicity. The literature is abounding with dramatic reports of adverse events related to colchicine use. In this regard, CKD patients may be at higher risk of being affected by colchicine toxicity. Thus, despite extensive liver metabolism [87], urinary excretion via both glomerular filtration and tubular secretion clears up to 20% of the drug [88]. Creatinine clearance of <25 mL/min portends a high risk of colchicine accumulation [1]. However, there is controversy and inconsistency regarding colchicine dose adjustment in CKD. All authors recommend significant dose reductions in patients with glomerular filtration rate (GFR) <50

mL/min/1.73 $m^2$. Some authors recommend complete avoidance of colchicine in patients with GFR <10 mL/min/1.73 $m^2$ and patients undergoing hemodialysis [6, 89]. However, these recommendations are not based on firm data. We recently studied the potential toxicity of colchicine under routine clinical practice conditions in 22 patients receiving long-term maintenance hemodialysis (>6 months, mean duration 8.9 ± 8.2 years) colchicine and 20 matched hemodialysis controls [90]. Four of 22 patients were using 0.5 mg/day, 4 patients were using 1.5 mg/day, and 14 patients were using 1 mg/day colchicine. There was no difference between the groups in terms of myo-neuropathic signs and symptoms, creatinine kinase and myoglobin levels, or blood counts except for white blood cell count, which was significantly higher in patients on colchicine treatment. Since this was not a randomized controlled study, bias cannot be excluded with certainty though. However, the study demonstrated that colchicine can be prescribed safely for those with advanced CKD for long periods of time.

Most of the reported toxicities in the literature had one or more "facilitating factors", such as renal and/or hepatic dysfunction [91] or concomitant use of other drug(s) [92–94] affecting metabolism of colchicine. Drugs that increase the risk of colchicine toxicity via dual modulation of ABCB1 (P-glycoprotein) and CYP3A4 include the macrolide antibiotics erythromycin and clarithromycin and statins, among many others [6]. Cyclosporin and tacrolimus may also modulate P-glycoprotein.

Colchicine toxicity is dose-dependent and characterized by 3 sequential and overlapping phases [95]. The first phase reflects gastrointestinal mucosal damage and is characterized by nausea, vomiting, and diarrhea. Symptoms quickly resolve upon dose reduction or drug discontinuation. The second phase is characterized by multiorgan dysfunction and metabolic derangements. Almost every organ system may be affected. Myopathy, neuropathy, and bone-marrow suppression are frequent [96–99]. Practically it is not possible to measure blood colchicine levels in every laboratory. The third phase is recovery.

Taken together, colchicine toxicity follows a predictable sequence of events and related symptoms and is potentially reversible when recognized early. When initiated with low doses and up-titrated according to clinical response along with close surveillance in informed patients, colchicine can be used safely even in patients receiving hemodialysis. The United States Physicians' Desk Reference® recommends the reduction of colchicine dose with estimated GFR (eGFR) between 30 and 50 mL/min/1.73 $m^2$ and 0.3 mg/day with clinical vigilance when eGFR is below 30 mL/min/1.73 $m^2$ [100]. The American College of Physicians' Drug Prescribing in Renal Failure booklet recommends 50–100% dose reduction with eGFR between 10 and 50 mL/min/1.73 $m^2$, whereas 25% of usual dose with eGFR <10 mL/min/1.73 $m^2$ [101]. On the other hand, British National Formulary 61 recommends avoidance of colchicine in patients with eGFR <10 mL/min/1.73 $m^2$ [102].

## Concluding Remarks

Colchicine has a broad range of anti-inflammatory and antifibrotic properties. In addition to its time-honored anti-amyloidotic effects, experimental and clinical data have disclosed anti-fibrotic effects both in kidney diseases and several other fibrotic disorders. Recent preclinical evidence of benefit in DN and renal mass reduction along with evidence for biological plausibility given the current understanding of the pathophysiologic pathways leading to kidney disease support the exploration of the role of colchicine in clinical studies. In this regard, randomized clinical trials are ongoing for DN. Decades of clinical experience and an ever-increasing range of indications make it likely that we will continue to see colchicine around for a long time.

## Author Contributions

All authors approved the final version of manuscript.

## Disclosure Statement

There is no conflict of interest between authors.

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