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Medicinal perspectives of colchicine and its derivatives: recent progress and challenges

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ABSTRACT

Various therapeutic effects have been found for alkaloids. However, severe side effects can limit the clinical applications of these bioactive compounds. Colchicine alkaloid as an anti-inflammatory agent can be used by oral administration to heal familial Mediterranean fever, gout disease, the management of pericarditis, neutrophilic dermatoses, and urticarial vasculitis. At high doses, multiple side effects involving gastrointestinal upset, rhabdomyolysis, and low blood cells are expected for this metabolite. In addition to the anti-inflammatory effect, anticancer and antimicrobial activities have been reported for this classical drug. Recent studies about drug delivery based on micro or nanosystems of colchicine showed promising aspects for side passing severe side effects. In this way, this review has tried to cover these studies focusing on advances and limitations for obtaining effective formulations.

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Introduction

Colchicine ($C_{22}H_{25}NO_6$) is an alkaloid, an anti-inflammatory agent employed via oral administration to treat familial Mediterranean fever, gout disease, and the management of pericarditis [1, 2]. In addition, this metabolite is applied off-label for neutrophilic dermatoses and urticarial vasculitis [3]. There are multiple side effects of colchicine including gastrointestinal upset, low blood cells, rhabdomyolysis, and the medication can be deadly at high doses [4]. There are several therapeutic effects including anti-inflammatory, anticancer, and antimicrobial effects for colchicine. Colchicine can decrease inflammation by promoting the exfoliation of the adhesion molecule L-selectin on the surface of endothelial cells and inhibiting the synthesis of superoxide in neutrophils [5]. Colchicine can be isolated from several plant species such as *Colchicum luteum* [6], *Colchicum autumnale* [7], and *Gloriosa superba* (Figure 1) [8]. Colchicine was isolated from several plant compounds (stems, seeds, leaves, and flowers) and its concentration was determined using high-performance liquid chromatography (HPLC). The corm had the highest percentage of colchicine (0.191 %) among all the investigated plant parts, followed by the seed (0.103 %). As a result, it can be said that *C. luteum* seeds and corms can be used as a natural source of colchicine for the pharmaceutical industry [9]. It should be noted that a comparison between monotherapy and combination therapy of this phytocompound with other therapeutic agents is critical for obtaining effective formulations [10]. In this review, we have tried to address the anti-inflammatory, anticancer, and antimicrobial effects of colchicine in micro and nanoformulations.

Anti-inflammatory activity

Colchicine is an old drug that is currently used to treat gout. However, colchicine has a wide range of anti-inflammatory activities, and studies suggest that it may be useful in a variety of other conditions [11]. The mechanisms by which colchicine exerts its anti-inflammatory properties are multiple. One of these mechanisms is the ability of colchicine to bind to free tubulin dimers, which, when incorporated into

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microtubules, can block subsequent microtubule polymerization. This dose-dependent mechanism, at least in vitro, is directly responsible for colchicine's effects on cytokine release, cell migration, and intracellular trafficking, and plays a critical role in colchicine's disruption of inflammatory cell activity [12].

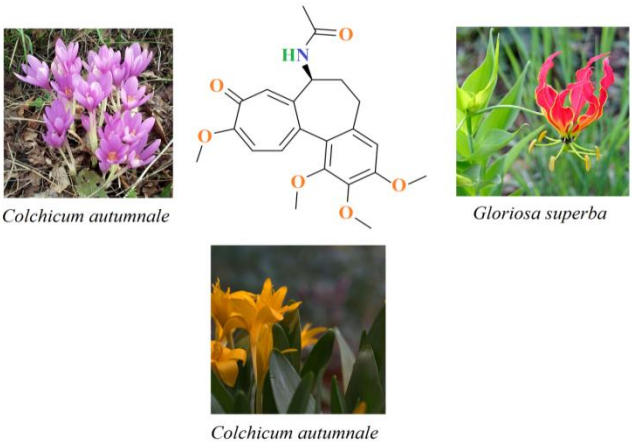

Fig. 1. The main plant source and chemical structure of colchicine [13].

The contribution of this mechanism to the effects of colchicine at clinical therapeutic doses is less clear. Colchicine modulates leukocyte-mediated inflammatory activities, including cytokine release, leukocyte production of superoxides, and various pyrogens [14]. The most famous mechanism of colchicine is the ability to bind to free tubulin dimers, which may lead to the inhibition of microtubule polymerization. This mechanism seems to lead to the cessation of the activity of inflammatory cells. In addition, colchicine can control inflammatory activities mediated by white blood cells (WBC). Therefore, it may target WBCs in general, leading to microtubule depolymerization, which in turn can inhibit WBC motility, phagocytosis, and degranulation. Colchicine may suppress the release of interleukin (IL)-1β and IL-18 by interacting with the inflammatory protein complex of the Nod-like receptor protein 3. Recently, colchicine has been validated to target several pathways concurrent with the hyperinflammation of Coronavirus disease 2019 (COVID-19) [15]. Moreover, this metabolite has a heart-protective effect and an anti-inflammatory effect toward rheumatoid diseases. As a niosomal emulgel nanoformulation, colchicine loaded on noisome (a diameter mean of 220.7 nm, a polydispersity index (PDI) of 0.22, and entrapment efficiency of 65.3%) based on jojoba oil (oil extracted from the seed of the *Simmondsia chinensis* (jojoba) plant) showed increased anti-inflammatory effects [16]. In the treatment and management of COVID-19, anti-inflammatory drugs are very important. Colchicine is one such drug that is used to treat auto-inflammatory diseases such as Mediterranean fever, Behçet's disease, and other rheumatic diseases. The effective mechanisms of the colchicine effect are the reduction of nuclear factor kappa B (NF-KB) complex activity and reduction of immune response and inflammatory genes such as NLRP3 (NOD-LRR (the nucleotide-binding oligomerization domain–leucine-rich repeat) and pyrin domain-containing protein 3), IL-1, Pro-IL-1β, IL-6, and tumor necrosis factor (TNF). Colchicine inhibits the activation of NLRP3 and Caspase-1. Colchicine inhibits the aggregation, development, and elongation of microtubules and can prevent the membrane-dependent functions required for the uptake, transmission, and replication of severe acute respiratory syndrome coronavirus 2 (SARS‑CoV‑2) (Figure 2) [17].

The anti-inflammatory effect of colchicine depends on the direct effect of colchicine on myeloid cells. However, Wang et al discovered a new mechanism of action of colchicine that depends on the secretion of the hormone growth/differentiation factor-15 (GDF-15) from the liver. Therefore, colchicine inhibits the activation of myeloid cells in mice by inducing hepatic GDF-15 secretion, but how GDF-15 mediates this anti-inflammatory activity is still unclear [18]. Another study reported that Bacopa monnieri (BM) supplementation reverses colchicine-induced dementia with its anti-inflammatory and antioxidant activity, suggesting that it may be an effective therapeutic intervention to improve the progression of Alzheimer's disease [19]. Colchicine is concentrated in leukocytes. Colchicine accumulates in much higher concentrations in leukocytes than in plasma, and the concentration inside leukocytes reaches its peak in about 48 hours, which corresponds to the maximum anti-inflammatory effects. Its anti-inflammatory properties lead to a wide range of therapeutic applications, including significant applications in the treatment of a wide range of skin diseases. Its mechanism of action and pharmacokinetics are largely unknown [20]. Inflammation plays a major role in the development

and progression of atherosclerosis. Although colchicine is considered an anti-inflammatory agent, it does not have the same mechanism of action as non-steroids. Clinical and experimental trials have investigated the anti-inflammatory activity of colchicine in atherosclerosis and coronary artery disease (CAD). Favorable results in recent clinical trials have generated considerable interest in further investigating the potential indications of colchicine in the treatment and prevention of CAD [21].

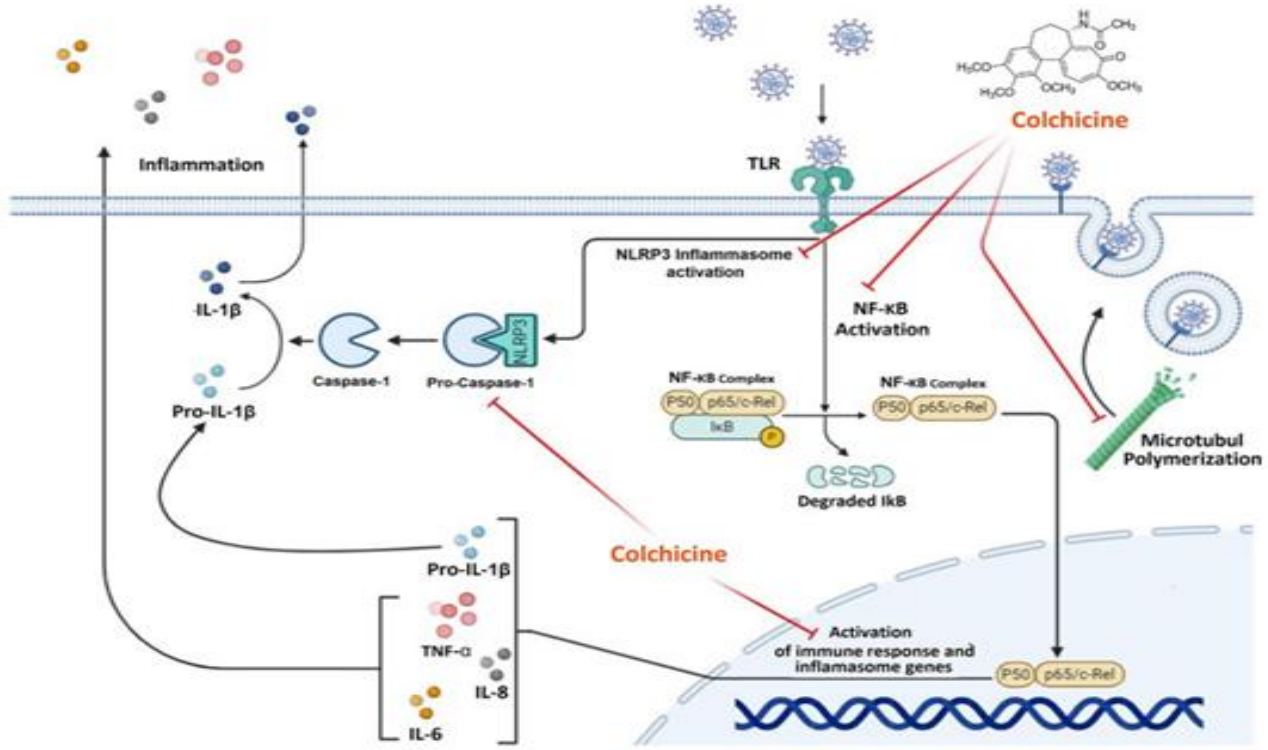

Fig. 2. Anti-inflammatory mechanisms of action of colchicine against COVID-19 infection (Extracted from [17]).

Anticancer activity

Although the anticancer activity of colchicine is not completely understood, it is reported that colchicine can inhibit microtubule dynamics and cell migration via polymerization blocking (Figure 3) [22, 23]. Furthermore, angiogenesis and metastatic cells are inhibited by colchicine in suitable concentrations. This metabolite via modulating the signal transduction pathway in microtubule polymerization has anticancer activity against osteosarcoma [24]. Colchicine administration significantly inhibited the growth of gastric carcinoma cells through the induction of caspase-3-mediated mitochondrial apoptotic pathways at a dose range of 0.05-0.1 mg/kg [25]. There are several colchicine derivatives with antitumor activity. For example, TCD (N-deacetyl-N-(chromone-2-carbonyl)-thiocolchicine) has been recognized as a potent anticancer agent against hepatocellular carcinoma cell lines at IC_{50} amount in the nanomolar [26]. The applications of organic and inorganic nanoparticles in the improvement of therapeutic effects of anticancer drugs cannot be ignored. Liposomes, tocosomes, niosomes, metal/metal oxide nanoparticles (NPs), lipid solid NPs, and mesoporous silica NPs (MSNs) are comment nanocarriers [27-30]. For instance, curcumin and colchicine in a core-shell structure were loaded on MSNs. Anticancer activity of these core-shell NPs was evaluated against several cancer cell lines including A-549 (non–small cell lung cancer), HOS (human osteosarcoma), MCF-7 (breast adenocarcinoma), and HCT-116 (colon carcinoma). Co-delivery nanoformulations exhibited higher anticancer activity compared to single delivery or free colchicine or curcumin. The highest and lowest anticancer effects were found against cell line HCT-116 and MCF-7, respectively. Promotion of apoptosis by increasing caspase-3, Bax, and p53 expression was indicated for anticancer mechanisms of this co-delivery nanosystem [31].

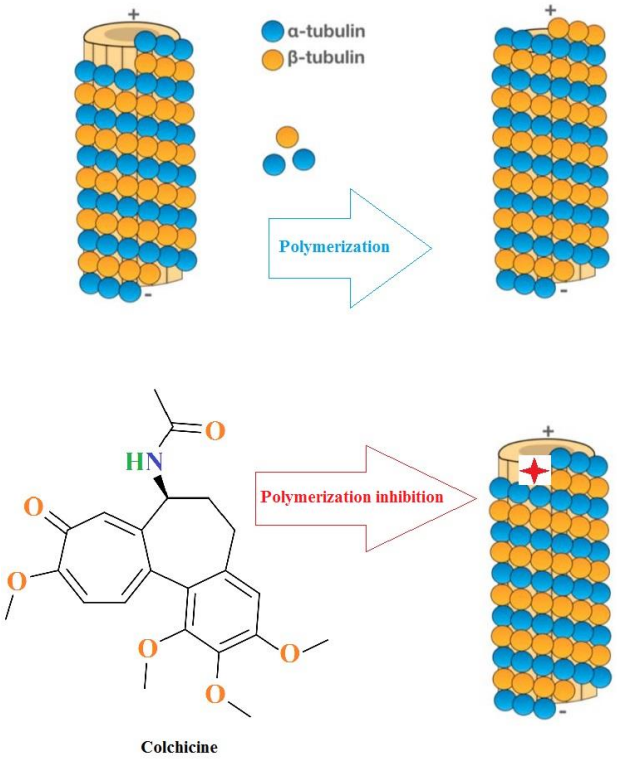

Fig. 3. Cholcicine can inhibit the polymerization process of tubulin [22].

Antimicrobial activity

The antimicrobial activity of several commercially available natural compounds such as colchicine, alkaloids, flavonoid derivatives, and simple phenolic acids has been screened, which showed significant antiviral activity against herpes simplex virus 1 (HSV-1) and lower antiviral activity against RNA virus parainfluenza (type-3). Phenolic compounds and alkaloids form unique patterns related to the desired biological activities. However, the antimicrobial activity depends on the specific substitution patterns in the chemical structures of the tested compounds. The data of this study show that natural compounds are the most attractive sources in the search for the discovery of new antimicrobial agents [32]. The combination of the trypanocidal drug benznidazole and colchicine showed cytotoxicity to infected cells and low antiparasitic activity. In contrast, the combination of the trypanocidal drug benznidazole and chloroquine significantly reduced Trypanosoma cruzi infection in vitro [33]. In traditional medicine, colchicine is used to treat gout. Several reports have exhibited colchicine can also be used in the treatment of COVID-19. The antiviral activity of this alkaloid is attributed to the inhibition of microtubule assembly and its ability to bind tubulin dimers, which can enhance anti-inflammatory effects and make colchicine a potent mitotic toxin. Colchicine may reduce pro-inflammatory cytokines and inhibit inflammatory signaling, a possible mechanism of COVID-19 pneumonia [34]. Gas chromatography-mass spectrometry (GC-MS) analysis showed the presence of an anticancer compound hydroxymethyl colchicine, antioxidant compound benzoic acid, and antimicrobial 2-(4-chlorophenoxy)-5-nitro in the endophytic fungal extract of *Vateria Indica* plant. Endophytic fungi of *Cladosporium* species isolated from *V. Indica* plant can be used as a potential source for the phytochemical anticancer hydroxymethyl colchicine, an antioxidant and antimicrobial benzoic acid 2-(4-chlorophenoxy)-5-nitro [35]. As the main antiviral activity against SARS-CoV-2, colchicine can prevent viral replication by disrupting microtubules [36].

Anti-diabetic

Several studies have been done to understand the relationship between colchicine as an anti-inflammatory agent and type 2 diabetes mellitus (T2DM) [37]. Colchicine reduced the risk of T2DM from 25 percent in non-users to 18.8 percent in users. Actually, according to the confirmed effect of anti-inflammatory drugs on T2DM, the rule of colchicine to reduce T2DM risk is justified [38]. One of the interesting abilities of colchicine is its ability to reduce insulin resistance and inflammation in adipose tissue in type 1 diabetes [39]. Also, colchicine can reduce the risk of acute forms of COVID-19 in diabetes diseases [40]. Another study has shown that neutrophil-related chronic inflammation (NRCI) in diabetic kidney diseases is reduced by colchicine through its anti-inflammatory ability [41].

Conclusions

As an important anti-inflammatory and anticancer mechanism, colchicine can inhibit microtubule dynamics and cell migration via polymerization blocking. In addition, angiogenesis, and metastatic cells may be hindered by colchicine in suitable doses. There are several colchicine derivatives such as TCD with potential anticancer activity. Co-delivery system of colchicine with another anticancer agent, particularly in nanoformulations can promote apoptosis

and anticancer effects. As an antiviral mechanism, viral trafficking and the formation of double-membrane vesicles have been blocked by colchicine. In general, nanocarriers such as liposomes, tocosomes, metal/metal oxide NPs, and MSNs may be applied for encapsulation or loading of colchicine.

Study Highlights

- Colchicine can inhibit microtubule dynamics and cell migration via polymerization blocking.
- Angiogenesis and metastatic cells may be hindered by colchicine in suitable doses.
- Viral trafficking and the formation of double-membrane vesicles have been blocked by colchicine.
- Nanocarriers such as liposomes, tocosomes, metal/metal oxide NPs, and MSNs may be applied for encapsulation or loading of colchicine.

Abbreviations

CAD: Coronary artery disease
COVID-19: Coronavirus disease 2019
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GC-MS: Gas chromatography-mass spectrometry
GDF-15: Growth/differentiation factor-15
HOS: Human osteosarcoma
HPLC: High-performance liquid chromatography
HSV-1: herpes simplex virus 1
IL: Interleukin
MSNs: Mesoporous silica NPs
MSNs: Mesoporous silica NPs
NF-KB: Nuclear factor kappa B
NLRP3: NOD-LRR (the nucleotide-binding oligomerization domain–leucine-rich repeat) and pyrin domain-containing protein 3
NPs: Nanoparticles
NPs: Nanoparticles
NRCI: Neutrophil-related chronic inflammation
PDI: Polydispersity index
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
T2DM: Type 2 diabetes mellitus
TCD: (N-deacetyl-N-(chromone-2-carbonyl)-thiocolchicine)
TCD: N-deacetyl-N-(chromone-2-carbonyl)-thiocolchicine
TNF: Tumor necrosis factor
WBC: White blood cells

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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