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Medicinal Importance of *Colchicum Candidum*- A Review

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Abstract Chemical analysis showed that *Colchicum candidum* contained many biologically active components. Nine alkaloids (3-demethylcolchicine, 2-demethylcolchicine, colchifoline, N-deacetyl-N-formylcolchicine, colchicine, cornigerine, 2-demethyldemecolcine, 3-demethyldemecolcine and demecolcine) were isolated from seven Colchicum species. Twenty phenolic compounds were also identified in extracts from five Colchicum species. The previous pharmacological studies showed that Colchicum candidum possessed antioxidant, antibacterial and acetylcholinesterase inhibitory effects, while, colchicine possessed antitumoral and antiinflammatory properties and has still kept its importance in the treatment of gout and many other diseases, such as familial Mediterranean fever (FMF), Behçet's syndrome, chirosis, psoriasis and many other dermatological diseases. This review was designed to highlight the pharmacological and therapeutic effects of *Colchicum candidum*.

Keywords Pharmacology, Therapeutic Effects, Toxicology, *Colchicum Candidum*

Introduction

Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and still the most widely practiced form of medicine in the world today. Plant showed wide range of pharmacological activities including antimicrobial, antioxidant, anticancer, hypolipidemic, cardiovascular, central nervous, respiratory, immunological, anti-inflammatory, analgesic antipyretic and many other pharmacological effects [1-30].

Old Greek physicians used the plant from which colchicine is derived as a therapeutic agent for gout, 3000 years ago. Middle age Arabic physicians also used the Colchicum to treat acute flares of gout**.** In India and Africa various preparations of colchicum are still used traditionally for gastroenterological, musculoskeletal and cutaneous diseases. Nine alkaloids (3-demethylcolchicine, 2-demethylcolchicine, colchifoline, N-deacetyl-N-formylcolchicine, colchicine, cornigerine, 2-demethyldemecolcine, 3-demethyldemecolcine and demecolcine) were isolated from seven *Colchicum* species. Twenty phenolic compounds were also identified in extracts from five *Colchicum* species. The previous pharmacological studies showed that *Colchicum candidum* possessed antioxidant, antibacterial and acetylcholinesterase inhibitory effects, while, colchicine possessed antitumoral and antiinflammatory properties and has still kept its importance in the treatment of gout and many other diseases, such as familial Mediterranean fever (FMF), Behçet's syndrome, chirosis, psoriasis and many other dermatological diseases. This review was designed to higlight the pharmacological and therapeutic effects of *Colchicum candidum*.

Plant Profile

Synonyms: *Colchicum balansae* Planch [31] .

Common Names:

Arabic: Mubasherat Elshata **English**: Naked ladies, Naked boys, False Autumn crocus[(32)].

Taxonomic Classification:

Kingdom: Plantae; **Phylum**: Magnoliophyta; **Class**: Liliopsida; **Order:** Liliales; **Family**: Colchicaceae; **Genus:** *Colchicum*; **Species**: *Colchicum balansae* [33].

Distribution

This species is distributed in the Mediterranean region and Greece to southern Turkey [34-35].

Description

Colchicum balansae is a variable species producing white to rosy-purple flowers in fall. Corm ovoid, up to 5 X 4 cm, tunics mostly coriaceous, finely ribbed outside, dark brown to blackish-brown, with a very long neck, at least 20 cm, frequently up to 50 cm long. Leaves 3-4, hysteranthous, crowded at ground level or slightly above, up to 30 X 6 (-9.5) cm, suberect to patent, mostly oblong, obtuse, flattish, not or shallowly plicate, with a sunken, rather distinct mid vein, slightly keeled, slightly undulate-twisted, thick, margins narrowly but distinctly cartilaginous, glabrous. Flowers 3-6 (-11), whitish or palest purplish-lilac, sometimes obscurely tessellated. Tube extremely long, whitish. Tepals up to 7 X 1.3 (-1.7) cm, unequal. Filament channels shallow, glabrous. Stamens 1 / 3-1 / 2 as long as tepals, at least outer ones inserted in perianth throat below connection of segments. Filament white, anthers yellow. Styles mostly distinctly overtopping stamens, white or sometimes purplish in upper part, thickened and curved at apex, stigmas decurrent. Capsules at ground level, up to 4 X 2 cm, oblong. Seeds red-brown to brown, raphe region swollen to a yellowish appendage [34].

Traditional Uses

In the 1st century AD Pedanius Dioscorides wrote (De Materia Medica) and stated that more than 3000 years ago Greek physicians used the plant from which colchicine is derived as a therapeutic agent for gout. Middle age Arabic physicians also used the Colchicum to treat acute flares of gout**.** In India and Africa various preparations of colchicum are still used traditionally for gastroenterological, musculoskeletal and cutaneous diseases [36-37].

Chemical Constituents:

A high-performance liquid chromatographic method was used to determine the colchicinoid alkaloids in Colchicum species. Nine alkaloids (3-demethylcolchicine, 2-demethylcolchicine, colchifoline, N-deacetyl-N-formylcolchicine, colchicine, cornigerine, 2-demethyldemecolcine, 3-demethyldemecolcine and demecolcine were isolated from seven *Colchicum* species. However, although many alkaloids have been identified in Colchicum. The major alkaloid of Colchicum is colchicine. All parts of Colchicum species have been shown to contain colchicine, but seeds and corms contained more colchicine than other plant parts. Numerous studies have been carried out by different researchers on colchicine and other chemical constituents of Colchicum species. Twenty phenolic compounds were also identified in extracts from five *Colchicum* species [35,38-39].

Pharmacological Effects

Acetyl cholinesterase inhibitory effect

Methanol extracts of the seeds of *Colchicum balansae* were investigated for their *in vitro* cholinesterase (AChE and BChE) inhibitory activity at 200 µg/ ml, using ELISA microplate assay. Acetylcholinesterase inhibitory activity possessed by the methanolic extracts of *Colchicum balansae* seeds extract (200µg/ml) was 10.90 ±1.17% and BChE inhibitory activity was 44.22 ±2.46% [40].

Many authors mentioned that Acetylcholinesterase inhibitors are the most effective approach to treat the cognitive symptoms of Alzheimer's disease. Althoudh acetylcholinesterase inhibitors was the most widely used medication in Alzheimer's disease treatment, but some report propound that acetylcholinesterase inhibitors have inclement side effects such as anorexia, diarrhoea, fatigue, nausea, muscle cramps as well as gastrointestinal, cardiorespiratory, genitourinary and sleep disturbances. Accordingly, medical field search for new acetylcholinesterase inhibitors with higher efficacy from natural sources. *Colchicum balansae* is one of the promising sources [41-42].

Antioxidant Effect

Methanol extracts of *Colchicum balansae* were investigated for antioxidant effect at 2000 µg/ ml by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity. Methanol extracts of *Colchicum balansae* displayed low effect in DPPH, below 40% [40].

The antioxidant properties of *Colchicum balansae* Planchon (CB) were investigated. The solvent extracts were prepared from CB tubers and leaves. Free radical scavenging activities were determined. Result of this study show that leaves extracts of CB exhibited higher antioxidant activity than tuber extracts with all types of solvent. The highest antioxidant activity efficiency was determined in extract leaf-ethanol (64%) and the least efficiency in extract tuber-benzine (14.5%). All extracts of CB tubers and leaves have effective free radical scavenging and reducing power. The highest free radical scavenging activity was determined in extract leaf-benzine (68.35%), followed by acetone (61.23%), methanol (58.67%) and ethanol extracts (54.74%) respectively. The highest radical scavenging activity was determined in extract tuber-benzine (61.28%), and the least efficiency in extract tuber-ethanol (20.48%). In addition, all extracts of CB tubers and leaves were determined as pyrocatechol equivalents [43].

Antibacterial Effect

The antibacterial properties of *Colchicum balansae* Planchon (CB) were studied. The results showed that *Colchicum* ethanol extract had a weak inhibitory effect against tested bacteria (*Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Enterococcus faecalis* ATCC 29212, *Klebsiella pneumoniae* ATCC 13883, *Escherichia coli* ATCC 25922, *Enterobacter cloacae* ATCC 23355, *Serratia marcescens* ATCC 8100, *Proteus vulgaris* ATCC 13315, *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium* ATCC 14028). *S. aureus* ATCC 25923 was more sensitive to ethanol extract (10 mm inhibition zone). When comparing the antimicrobial activity of the control antibiotics, the ethanol extract exhibited lower antimicrobial activity [43].

Pharmacology of Colchicine

Colchicine has been found to possess antitumoral and antiinflammatory properties and has still kept its importance in the treatment of gout and many other diseases, such as familial Mediterranean fever (FMF), Behçet's syndrome, chirosis, psoriasis and many other dermatological diseases [44].

Colchicine was antigout agent, produced no analgesic effect, not a uricosuric, and will not prevent progression of gout to chronic gouty arthritis. Its mechanisms of action involved reducing inflammatory response to the deposited crystals, diminishing phagocytosis and suppressing monosodium urate crystal-induced NACHT-LRR-PYD-containing protein-3 (NALP3) inflammasome-driven caspase-1 activation, IL-1b processing and release, and L-selectin expression on neutrophils. Its prophylactic, suppressive effect helped reduce the incidence of acute attack. It was a good alternative to NSAIDs, and probably as effective. It was of value in patients with heart failure since unlike NSAIDs it did not induce fluid retention, also it can be given to patients receiving anticoagulants [45-46].

Furthermore, colchicine possessed anti-inflammatory, it reduced mobility, adhesiveness, and chemotaxis of polymorphonuclear cells. It interfered with intercellular adhesion molecules, selectins, thus inhibiting T-lymphocyte activation and its adhesion to endothelial cells. It impaired cellular secretion of procollagen and increased collagenase production that promoted a larger collagenolytic action [47-49].

Colchicine also exerted immunosuppressive action, It inhibited cell-mediated immune responses, by inhibiting immunoglobulin secretion, IL-1 production, histamine release and HLA-DR expression [50].

Colchicine was effective and safe for the treatment and prevention of recurrent pericarditis and might ultimately serve as the initial mode of treatment, especially in idiopathic cases. Colchicine plus conventional therapy led to a clinically important and statistically significant benefit over conventional treatment, decreasing the recurrence rate in patients with a first episode of acute pericarditis [51].

Antitumor activity of colchicines was mediated by interfering with cell division through its disruptive action on the mitotic spindle. Evidence for this was obtained from molecular studies and isolation of the remnants of the mitotic apparatus of colchicine- treated cells. This inhibition occurred as direct and indirect action. A direct action involved binding of colchicine to spindle fibers causing them to dissociate into protein subunits, while, indirect action was mediated by activation of an enzyme which attacked the spindle. Furthermore, colchicine reversibly interacted with a set of sites within the cell and mitosis will inhibited if a critical fraction of these sites were occupied by colchicines [52].

Colchicine was found to be effective in Behcet's syndrome. It was postulated that by blocking phagocytosis, colchicine may increase superoxide scavenging activity of neutrophils which was impaired in this syndrome [53-55].

In the treatment of dermatological diseases, colchicine showed effectiveness in psoriasis in many clinical trials [56-61]. Sweet's syndrome also improved with a daily dose of 1.5 mg colchicines [62]. Colchicine also used at the dose of 1.2-1.8 mg/day to treat patients with dermatitis herpetiformis, it appeared as a good alternative in those who could not take sulfonamides [63]. It appeared that colchicine also a successful treatment of epidermolysis bullosa acquisita [64], and in chronic bullous dermatosis of childhood with G6PD deficiency [65]. It was also beneficial in leucocytoclastic vasculitis and urticarial vasculitis [66], scleroderma and amyloidosis [67-68].

Many other dermatological diseases were also treated with colchicines including erythema nodosum leprosum, pyoderma gangrenosum, severe cystic acne, calcinosis cutis, keloids, sarcoid, condyloma acuminata, fibromatosis, relapsing polychondritis, primary anetoderma, subcorneal pustular dermatosis, erythema nodosum, scleredema, and actinic keratosis [69].

It also possessed other pharmacological effects including, decrease of the corporal temperature, depression of the respiratory center, increased response to sympathomimetic agents, contraction of blood vessels, hypertension by central vasomotor stimulation, and alteration of the neuromuscular function [69].

Colchicine was the gold standard and indeed the only recommended drug for treating familial Mediterranean fever (FMF). It was thought to primarily concentrated in neutrophils and inhibit their increased chemotactic activity during FMF attacks [70].

It was an effective drug for eliminating the attacks and preventing the development of amyloidosis in patients with familial Mediterranean fever (FMF) [71].

Colchicine should be administered orally once the diagnosis of FMF is confirmed (or as a therapeutic trial in establishing the diagnosis). Adult dosing is 1.2–2.4 mg/day, whereas children usually start at 0.3–1.2 mg/day according to age and weight and can increase sequentially up to 2 mg/day depending on how effectively the attacks were regulated [72].

Side Effects and Toxicity

The side effects of the plant were attributed to colchicines toxicity: A first oral dose of colchicine 0.5 mg/kg causes diarrhea and/or vomiting in up to 15% of patients; these side effects occur early but are generally mild, and may resolve with dose reduction. Adverse effects with long term therapy: 5-10% of patients underwent gastrointestinal side effects, (diarrhea, bloating and vomiting). However, colchicine caused wide range of side effects including: nausea, vomiting, diarrhea, burning sensation in throat, burning sensation in stomach, burning skin sensation, severe diarrhea, hemorrhagic diarrhea, paralytic ileum, dehydration, hypotension, shock, multiple organ failure, CNS toxicity and confusion, bone marrow damage, hepatocellular damage, muscle damage, neuropathy, respiratory distress, myocardial depression, renal damage, toxic epidermal necrolysis-like reaction, pancytopenia, respiratory depression, cardiovascular collapse and sepsis [37]**.**

Conclusion

This review discusses the chemical constituent, pharmacological and therapeutic effects of *Colchicum candidum* as promising herbal drug because of its safety and effectiveness.

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