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Importance of *Colchicum* species in modern therapy and its significance in Turkey

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Abstract: *Colchicum* species, which are widely used as medication for many years, still remain important in treatment. Some of them are cultivated to be used for pharmaceutical industry. Tropolone alkaloids content of the species help in the treatment of FMF, gout, amyloidosis, cirrhosis, Behcet's disease, psoriasis, Hodgkin lymphoma, myeloid leukemia and skin cancers. An economic and efficient synthesis method of *Colchicum* alkaloids haven't found yet, that's why colchicine and other alkaloids are obtained from plant source by extraction. The wide variety of *Colchicum* species in Turkey lead the researchers to investigate new sources of *Colchicum* rich in tropolone alkaloids. In our department, *Colchicum* species have been studied for more than 45 years and the contents and biological activities of the *Colchicum* species growing in our country are continuing to be studied today. This review was performed to summarize the investigations on *Colchicum* species in the world and to emphasize its importance in Turkey.

Key words: *Colchicum*, tropolone alkaloids, colchicine, anticancer, gout, antiinflammatory

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Introduction

Usage of plants for treatment is as old as mankind itself. Some of these plants have still been used for the treatment of various diseases. One of the most important medicinal plants are *Colchicum* species, which have been used for centuries to treat several disorders (Le Hello, 2000). Name of *Colchicum* is referring to "Colchis" an ancient region on the Black Sea, and indicates its origin. *Colchicum* species commonly known as autumn crocus, meadow saffron or naked lady which had been known as Hermodactyl, Sürinjan, Kolkikon in Anatolia (Baytop, 1999; Sapra et al., 2013) .

Botanical properties of the officinal species *Colchicum autumnale* L. was first described by Dioscorides in the first century BC and its extract was recommended for the treatment of gout in *De Materia Medica* (Sapra et al., 2013). Despite its toxicity, seed extracts of *C.autumnale* were prescribed by many doctors. Corms and seeds of the plant were listed in London Pharmacopoeia in 1639 that increase the importance of the species (Sütlüpınar, 1983). Colchicine, the major alkaloid from *Colchicum autumnale* was first isolated by two French pharmacists PJ. Pelletier and JB. Caventou, in 1920 (Ben-Chetrit & Levy, 1998; Levy et al., 1991). The configuration and of colchicine was determined by several workers (Anjum & Brossi, 1991; Capraro & Brossi, 1984). Understanding of whole chemical structure lead to investigate pharmacological activities of Colchicine (Larsson & Ronsted, 2014).

Colchicum is a valuable genus whose species are rich in alkaloids especially colchicine. Many studies showed that it possesses antitumoral and antiinflammatory activity (Brossi, 1990; Kiraz et al., 1998; Ueda et al.,1987; Wetherley Mein et al., 1983) Colchicine has a great potential as an anticancer drug but it has narrow therapeutic index (Wallace et al., 1991). Hence, derivatives of Colchicine were investigated as anticancer agents, some of them have been found possessing antitumoral activity as much as itself and also being less toxic (Cifuentes et al., 2006; Graening & Schmalz, 2004). Especially demecolcine and trimehyl colchicine acid methyl ester have been evaluated as antileukaemia agents.

An important antiinflammatory agent along with its anticancer activity, colchicine is frequently used in gout disease, FMF (Familial Mediterranean Fever) amiloidosis, cirrhosis, Behçet's disease and psoriasis (Cocco et al., 2010). It is also used in fruit and flower cultivation thanks to its chromosome duplicating ability helping to grow bigger products (Sütlüpınar, 1983).

Most of the semi-synthetic derivatives of colchicine are used in modern medicine nowadays. Thiocolchicoside, derived from 3-demethylthiocolchicine, is used for its myorelaxant effect in recent years (Kayaalp, 2002).

Although many different *Colchicum* species grow wild in Turkey, the major source of tropolone alkaloids, *Colchicum autumnale*, does not.

Botany and distribution of *Colchicum* species

The genus *Colchicum* belongs to the family Colchicaceae (previously Liliaceae). While the species number is constantly changing approximately 100 species of the genus *Colchicum* is distributed unequally around the world (Dinç-Düşen & Sümbül, 2007). *Colchicum* species are taxonomically very difficult group particularly autumn-flowering species (Alexiou, 2013).

Colchicum species are divided into two groups according to flowering time. Flowers and leaves occur at different seasons. While flowering is in autumn, leaves and fruits appear in spring (hysanthous). In contrast, on spring-flowering species, flowers and leaves appear together (synanthous). Autumn-flowering species usually have bigger corm and seed than spring-flowering ones (Sütlüpınar, 1983).

Turkey is a major centre of diversity and speciation with the high endemism rate. In Turkey, approximately 50 species of *Colchicum*, grow naturally, 22 of which endemic (Güner et al., 2000). Autumn and spring flowering species from Turkey are given in Tables 1a and 1b.

Table 1a. Autumn-flowering species from Turkey

Autumn-flowering species in Turkey			
Colchicum balansae	*Colchicum decaisnei*	*Colchicum lingulatum subsp. rigescens*	*Colchicum soboliferum*
Colchicum baytopiorum	*Colchicum dolichantherum*	*Colchicum macrophyllum*	*Colchicum speciosum*
Colchicum bivonae	*Colchicum heldreichii*	*Colchicum micaceum*	*Colchicum stevenii*
Colchicum boissieri	*Colchicum hirsutum*	*Colchicum micranthum*	*Colchicum szovitsii subsp. branchyphyllum*
Colchicum chalcedonicum subsp. chalcedonicum	*Colchicum ignescens*	*Colchicum paschei*	*Colchicum turcicum*
Colchicum chalcedonicum subsp. punctuatum	*Colchicum imperatoris-frederici*	*Colchicum persicum*	*Colchicum umbrosum*
Colchicum chlorobasis	*Colchicum inundatum*	*Colchicum poryphyllum*	*Colchicum variegatum*
Colchicum cilicicum Colchicum davisii	*Colchicum kotschyi Colchicum kurdicum*	*Colchicum sanguicolle Colchicum sieheanum*	

Table 1b. Spring-flowering species from Turkey

Spring-flowering species in Turkey			
Colchicum antepense	*Colchicum figlalii*	*Colchicum minutum*	*Colchicum szovitsii*
Colchicum atticum	*Colchicum lagotum*	*Colchicum munzurense*	*Colchicum szovitsii subsp. szovitsii*
Colchicum burttii	*Colchicum leptanthum*	*Colchicum raddeanum*	*Colchicum trigynum*
Colchicum crocifolium	*Colchicum manissadjianii*	*Colchicum serpentinum*	*Colchicum triphyllum*

Chemical composition of *Colchicum* species

Colchicum is a valuable genus whose species are rich in alkaloids especially Colchicine (Figure 1). *Colchicum* species also contain flavonoids, phenolic acids, tannin, fatty acids (Evans, 2002) . For a long time, colchicine was thought to be the only active compound of *C.autumnale* but investigations on both *C. autumnale* and other *Colchicum* species showed the existence of many other active tropolonic alkaloids (Alali et al., 2005; 2007; 2010; Capraro & Brossi, 1984).

The alkaloids of species were classified under different groups such as phenethylisoquinoline type, homoproaporphine type, homoaporphine type, androcymbine type, colchicine type, allocolchicine type, lumicolchicine type, homoerythrinan type (Larsson & Rønsted, 2014).

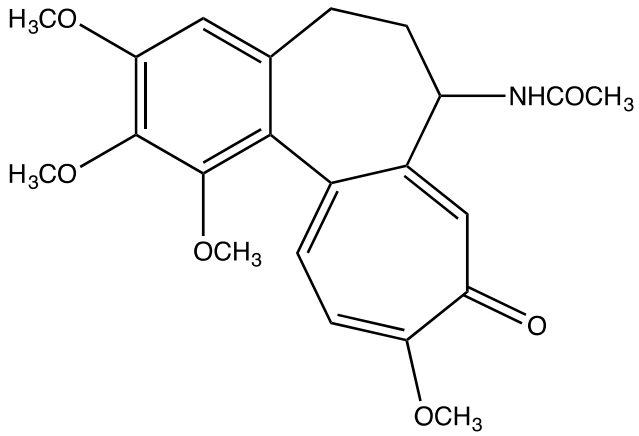

Figure 1. Colchicine

Colchicine is a protoalkaloid with a benzocycloheptanotropolone as the main ring. The alkaloids possessing this ring structure are usually named as 'tropolone alkaloids'. Colchicine is an tropolone alkaloid which occurs as yellowish-white amorphous scales with a very bad bitter taste (Capraro & Brossi, 1984).

Acetamide group is connected to the nitrogen out of the ring in colchicine. This acetamide group is connected to the cycloheptane of the benzocycloheptanotropolone ring system carrying 4 metoxyls. Here, tropolone, is a seven-membered, unsaturated ring that carries a keton group. 3 of the 4 methoxyl groups are connected to benzene, the other is connected to the tropolone ring.

There is an important structure-activity relationship in tropolone alkaloids. Colchicine and its derivatives are sensitive to light and when affected by light, are converted to lumi derivatives. Studies showed that there is no antitumoral activity when the tropolonoid structure is destroyed (Capraro & Brossi, 1984; Sapra et al., 2013).

Among the alkaloids of *Colchicum* species, one of the most important alkaloid is demecolcine, which is used for treatment of myelocytic leukemia and malignant lymphoma. Demecolcine possesses antitumoral activity like colchicine with low toxicity that makes it valuable as a medicine (Gupta, 1985; Rodríguez-Arnaiz, et al., 2004).

It is observed that the major phenolic acid and flavon compounds are benzoic acid and its derivatives, vanilic acid, vanillin, vanilic acid, coumaric acid, caffeic acid, ferrulic acid, luteolin and apigenin (Pırıldar et al., 2010). Caffeic acid and luteloin are the primary compounds in terms of phenolic compounds in the *Colchicum* species studied. 2-hydroxy-6methoxybenzoicacid only occurs in plants Wurmbaeoideae subfamily, this carries importance for chemotaxonomic identification (Husek et al., 1990).

Pharmacological effects of Colchicine

Colchicine has plenty of mechanism and many of them are complex. The main known mechanism of the colchicine, is its effectiveness of binding tubulin and inhibiting microtubules polymerization. According to studies, *Colchicine* is a great antimitotic agent likewise Vinca alkaloids (Levy et al., 1991). There is vast literature on biological activities of many *Colchicum* species and their major alkaloid colchicine.

Biological importance of *Colchicum* species were attributed for their tropolonic alkaloids particularly colchicine. Tropolonic alkaloids possess similar pharmacological activities. Differences of their chemical structure affect biological activities, such as increasing, decreasing or removing activities (Le Hello, 2000; Sapra et al., 2013). Today, colchicine has great importance to treat some diseases alone or combined with other drugs and commercially are prescribed throughout the world.

Methanol extracts prepared from the seeds and corms of *Colchicum* species were tested for their cholinesterase inhibition activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which are related to Alzheimer's disease, using ELISA microplate reader in 200 $\mu g/ml^{-1}$. In addition to this, antioxidant activity of the extracts were measured for their scavenging activity with 2000 $\mu g/ml^{-1}$ concentration of 2,2-Diphenyl-1-picrylhydrazyl (DPPH). While most of the extracts exhibited no activity, *C. variegatum* (%35.50 +2.26)'s methanol extract demonstrated mediocre activity. *C. crocifolium* (%82.73 +1.8) and *C. variegatum* (%67.71 +2.79) showed prominent activity. Along with this, all extracts were determined for their DPPH scavenging activity below % 40 (Sevim et al., 2010).

Low concentrations of colchicine (0.1 mg/ml) proved efficient in killing malign lymphoid cells without affecting normal lymphocytes *in vitro* studies. While small and large lymphoma cells were exterminated in experimental environment, lymphocytes at reactive lymph nodes survived. In this way, colchicine was used as an instrument for histologic diagnosis of lymphoma. Only one false negative and two false positive were acquired by using colchicine sensitivity > 30 % criterion in standart histologic examination of 31 lymphomatous and 30 reactive adenopathy. (Wetherley Mein et al. 1983)(Schrek et al. 1976) (Le Hello, 2000). In a PhD thesis study realized in our department, it was revealed that all methanol extracts from different parts of *C. baytopiorum* displayed high cytotoxic activity using MTT method on K562 (Chronic myeloid leukemia cell line) and HL60 (Promyeloid leukemia cell line) (Pırıldar et al., 2010).

In a study carried out on rats, it was shown that colchicine reduced the urinary excretion of Tamm-Horsfall protein, altered its structure and thus prevented it to form a complex with Bence-Jones protein (Sanders 1993). This aggregation is the reason of acute renal failures in myeloma patients. In contrast to these promising experimental results, Tamm-Horsfall protein

levels in the serum and urine of 6 healthy volunteers showed no change despite colchicine administration for 6 days (Cairns et al., 1994). In order to investigate the effects of colchicine and silymarin on liver, doses of colchicine or silymarin were administered on rats with liver damage, at the end of study the results showed that both compounds exhibited similar hepatoprotective action against chronic liver damage (Favari and Pérez-Alvarez 1996). Colchicine was applied for 12 months on rats with CCI_4 induced cirrhosis and a decrease in cirrhosis tissue generation was observed in all of the rats (Le Hello, 2000).

The usage of colchicine in gout treatment was approved in 1987 with a double-blind placebo controlled study. A dramatic decline in complaints of patients on colchicine by 18-30 hours was monitored comparing to placebo-administered patients. Diarrhea occured in almost every patient on colchicine before the decrease of complaints in 24 hours. Colchicine, compared to the other anti-inflammatory drugs, still had the least side effects (Ahern et al., 1987). Patients with chronic gout arthiritis on allopurinol treatment were seperated into two groups. One was administered 0.6 mg of colchicine twice a day, the other group was administered placebo for 3 months in a randomized double-blind study. First group, which were on both allopurinol and colchicine treatment has seen a significant decrease in acute gout crisis (Borstad et al., 2004). In a double-blind placebo controlled study aiming to evaluate the effects of colchicine treatment, 2 groups of 10 FMF patients were orally administered either 0.6 mg colchicine or placebo 3 times a day for a period of 6 months. Chronic colchicine treatment was given for the purpose of suppressing the painful febrile attacks. In 9 patients on placebo treatment 59 attacks were observed, while in colchicine-treated patients this number was only 2 patients with 5 attacks. These results are statistically significant ($P<0.002$) and prove that continuous colchicine treatment is efficient in preventing attacks (Goldstein & Schwabe, 1974).

Colchicine has been recommended to treat and prevent serositis in patients with familial Mediterranean fever. In a study, three hundred fifty children (younger than age 16) who had familial Mediterranean fever (FMF) were given treatment with colchicine (1-2 mg / day) for 6-13 years. Complete remission of attacks in 64 % and partial remission in 31 % of treated pediatric patients was observed. None of the children developed amyloidosis while on the colchicine regimen and the side effects of colchicine were mild (Zemer et al., 1991). The results of a study to

evaluate the outcome of pregnancies of normal women married to men with familial Mediterranean fever, some of whom took colchicine during the conception with their wives indicated that neither FMF nor colchicine increases the rate of abortions or congenital malformations (Ben-Chetrit et al. 2004). Colchicine was also recommended as a first-line treatment for recurrent pericarditis (class 1 indication) in the 2004 guidelines of the European Society of Cardiology. In 2005, an open-label, randomized trial, the colchicine for Recurrent Pericarditis (CORE) study, showed a benefit of colchicine in the treatment of pericarditis. In a multicenter, double-blind, randomized trial, the use of colchicine in addition to conventional antiinflammatory therapy significantly reduced the rate of incessant or recurrent pericarditis, as compared with placebo. The possible beneficial effect of colchicine, in non-insulin dependent diabetes mellitus (NIDDM) WAS studied. It was seen that colchicine could significantly reduce blood glucose levels, both fasting and post-prandial when given at a dose of 0.5 mg thrice a day in NIDDM patients. This study suggests that colchicine has anti-diabetic properties (Das, 1993).

Antiinflammatory drugs may be useful in the treatment of Alzheimer disease (AD). 20 patients with AD were treated with hydroxychloroquine 200 mg twice daily for 11 weeks, or hydroxychloroquine 200 mg twice daily plus colchicine 0.6 mg twice daily for 12 weeks and patients were monitored for adverse medical, cognitive or behavioral effects. There were no significant side effects in both of the groups but 2 subjects receiving the two drugs together experienced diarrhea. It was found that these regimens of antiinflammatory therapy are well-tolerated in patients with Alzheimer disease (Aisen et al., 2001). In a randomized, double-blind, placebo-controlled crossover trial, it was studied with a total of 16 patients with chronic idiopathic constipation to determine if colchicine will increase spontaneous bowel movements. Patients received either colchicine 0.6 mg or a placebo for 4 weeks and recorded their daily number of bowel movements and daily symptoms of daily nausea, abdominal pain and bloating. It was concluded that Colchicine may be an effective agent available to treat patients with chronic constipation who are refractory to standart medical therapy (Verne 2003).

Colchicine is widely used in Behçet's syndrome. The effectiveness of colchicine in a 2 years randomized, double-blind, placebo-controlled study among a larger group of patients of both sexes was assessed and

and it was found that colchicine has different manifestations of Behçet's syndrome. Its efficacy was not the same between the male and female patients. colchicine was clearly effective for arthritis in both sexes. Significant beneficial effects of colchicine on erythema nodosum has been shown, with a marked beneficial effect of colchicine in the genital lesions amog the female patients (Yurdakul et al., 2001).

Twenty-two psoriatic patients were treated orally with colchicine, at a dosage of 0.02 mg per kg per day for a duration of 2-4 months. Complete clearing or marked improvement were noted in 8 of the 9 patients who had the predominant type of lesion (Wahba & Cohen, 1980).

Investigations on *Colchicum* species in Turkey

Many research groups have examined different *Colchicum* species for their alkaloid content (Alali & Tawaha, 2007; Al-Fayyad et al., 2002; Khan, et al., 2011; Santavy et al., 1983; Ondra et al., 1995). In 1970, Prof. Turhan Baytop and Gunay (Özcöbek) Sarıyar started the studies on *Colchicum* species in our department and it has been continued by Nurhayat Sütlüpınar to our day (Baytop & Özcöbek, 1970; Husek et al., 1990; Sütlüpinar et al., 1988). The studies on *Colchicum* species have still being worked by our group. In all of these studies, quantitative analysis and isolation work have been carried out on many *Colchicum* species growing in Turkey. Chemical composition of some *Colchicum* species from Turkey which were studied before are summarized in Table 3.

Table 3. Alkaloids and phenolic composition of *Colchicum* species in Turkey

Species	Parts	Alkaloids		Phenolic compounds	
C.baytopiorum (Pırıldar et al. 2010)	Flower Leaf Seed Corm	Colchicine Demecolcine 2-demethylcolchicine 3-demethylcolchicine *N*-deacetyl-*N*-formylcolchicine	Colchifoline 2-demethylcolchifoline 2-demethyl-γ-lumicolchicine 2-demethyldemecolcine	Benzoic acid and derivatives Coumaric acid Caffeic acid	Ferrulic acid Luteolin Vanillic acid
C.bivonae (Orhon et al.,, 1982)	Seed Corm	Colchicine Demecolcine β-Lumikolşisin γ-Lumikolşisin 2-demethylcolchicine 3-demethylcolchicine Cornigerine *N*-deacetyl-*N*-formylcolchicine	2-demethyldemecolcine *O*-methylkreysigine Colchiciline *N*-deacetyl-*N*-formylcolchicine *N*-deacetylcolchicine 2,3-didemethylcolchicine	-	
C. bornmuelleri (Ondra et al.,1995a)	Flower Leaf Seed Corm	Colchicine Demecolcine 2-demethylcolchicine 3-demethylcolchicine Cornigerine	Colchifoline *N*-deacetyl-*N*-formylcolchicine 2-demethyldemecolcine 3-demethyldemecolcine	Benzoic acid and derivatives Coumaric acid Caffeic acid	Ferrulic acid Luteolin Vanillic acid
C. kotschyi (Ondra et al.,1994a)	Leaf Seed Corm	Colchicine Demecolcine 2-demethylcolchicine 3-demethylcolchicine	Colchifoline 2-demethyldemecolcine 3-demethyldemecolcine	Benzoic acid and derivatives Coumaric acid Caffeic acid Vanilin	Ferrulic acid Luteolin Vanillic acid 3,4-dihiydroxibenzaldehyde
C.macrophyllum (Ondra et al.,1994b)	Flower Leaf Seed Corm	Colchicine Demecolcine 2-demethylcolchicine 3-demethylcolchicine Colchifoline	*N*-deacetyl-*N*-formylcolchicine 2-demethyldemecolcine 3-demethyldemecolcine	Benzoic acid and derivatives Coumaric acid Caffeic acid	Ferrulic acid Luteolin Vanillic acid 3-(4 methoxyphenyl)-propanoic acid

C. speciosum (Ondra et al.,1995b)	Flower Leaf Seed Corm	Colchicine Demecolcine 2-demethylcolchicine 3-demethylcolchicine Cornigerine	Colchifoline *N*-deacetyl-*N*-formylcolchicine 2-demethyldemecolcine 3-demethyldemecolcine	Benzoic acid and derivatives Coumaric acid Caffeic acid Sinnamic acid	Ferrulic acid Luteolin Vanillic acid
C. triphyllum (Ondra et al.,1995)	Flower Leaf Seed Corm	Colchicine Demecolcine 2-demethylcolchicine 3-demethylcolchicine Cornigerine	Colchifoline *N*-deacetyl-*N*-formylcolchicine 2-demethyldemecolcine 3-demethyldemecolcine	Benzoic acid and derivatives Coumaric acid Caffeic acid	Ferrulic acid Vanillin Vanillic acid
C.turcicum (Baytop &Özcöbek, 1970; Husek et al., 1990)	Flower Leaf Seed Corm	Colchicine Demecolcine 3-demethylcolchicine β-Lumicolchicine Colchifoline	Cornigerine *N*-deacetyl-*N*-formylcolchicine 3-demethyldemecolcine	-	
C.umbrosum (Sütlüpınar et al.,2015)	Seed	Colchicine Demecolcine Colchifoline Colchiciline Colchicoside	3-demethylcolchicine *N*-deacetyl-*N*-formylcolchicine 4-hydroxicolchicine	-	

The results of the studies revealed that the chemical composition of Turkish *Colchicum* species are comparable to that of *C. autumnale*.

Conclusion and Future studies on *Colchicum* species

Colchicum species have been of great economic importance from past to present due to their properties in medicine.

Due to the high level of toxicity of colchicine, the synthesis and isolation studies mostly aim to find derivatives with similar effects but showing lower toxicity.

There is vast literature for synthesis methods of colchicine but none of them are economical due to their complex procedure. Researchers all around the world focus to find an economic way to produce synthetic colchicine.

Lately, *C.autumnale* does not answer the demands. In the light of recent studies, it is revealed that *C. speciosum*, growing natively in northeast Turkey, is very rich in colchicine alkaloids and seeds of this species have begun to be exported for colchicine isolation.

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