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Molecular, Biological and Content Studies on *Colchicum* L. Species

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Abstract

Colchicaceae family of the genus *Colchicum* L. is in the 39 taxa present in Turkey which 18 are endemic. The Colchicine compound found in *Colchicum* species was obtained in the past, but its structure was not fully found. In the following years, this substance was developed further and reached today and was used in the treatment of diseases such as gout, rheumatism, asthma and dysentery. These species were investigated in terms of phylogenetic analysis, phytochemical content and biological activities. In many phytochemical studies, there are studies in which colchicine and its derivative compounds, which are alkaloids, have been isolated. Many antioxidant and total secondary metabolite quantification experiments such as DPPH free radical scavenging activity, metal chelation, FRAP, CUPRAC, determination of total phenolic assays were carried out on different solvent extracts of *Colchicum* species. In studies using extracts of these species, some observed that it has antioxidant enzyme inhibitory activity. The antimicrobial activities of the extracts tested on different bacterial strains have been reported. Apart from these studies, different cell lines were used on different strains of this species and their cytotoxic results were compared. The effects of colchicine obtained from *Colchicum* species on various diseases were investigated. In this review, detailed information is given about phylogenetic analysis, phytochemical, pharmacological and biological activity (antioxidant, antioxidant enzyme inhibitor, anti-inflammatory, antimicrobial, cytotoxic) studies.

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1. INTRODUCTION

Plants have been used for medicinal purposes since the earliest times. Turkey has an important plant diversity because of its geographical location. *Colchicum* L. geophyte plant species, Turkey will contribute to the evaluation of the plant has been important in this review. Endemic species unique to Turkey is an important part of plant diversity. Belonging to Colchicaceae is present in Turkey 39 taxa including 18 endemics (Tüyel *et al*., 2020). *Colchicum* L. (Colchicaceae), which is popularly named by different names such as Aliöksüz, Öksüzali, Öksüzoğlan, Kar Çiçeği, Güzçiğdemi, Göçkovan, Kalkgit, Vargit and Morca, belongs to the Colchicaceae family (Baytop, 1994; Kaya, 2011). Plants belonging to the Colchicaceae family have been used as ornamental plants in parks and gardens due to their medicinal and aromatic properties as well as their elegant and beautiful appearance (Metin *et al*., 2014). Members of this family comprise perennial plants with six leaves, hypogene flowers and specialized underground structures (Kılıç *et al*., 2014). Underground structures are lumpy, corm

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and stony. The tubers are wrapped in tunica and the tunica runs along with the tuber above the ground. The leaves are flat or lanceolate and disappear after the seeds ripen. The flowers are generally purplish-pink, pink and white. Some of the blooming periods of this species take place in spring and some in the fall period (Sütlüpınar, 1981). *Colchicum* is a very important plant used to treat diseases in medicine, thanks to the tropolone alkaloid it contains. There is even evidence that *Colchicum* is used in medicine (Tüyel, 2015). Colchicine was obtained in 1820. However, its exact structure was not discovered until 1950. In the past, colchicine has been used in the treatment of diseases such as gout, rheumatism, asthma and dysentery (Düşen & Sümbül, 2007; Kılıç *et al*., 2014; Suica-Bunghez *et al*., 2017; Ahmad, 2010; Gökel *et al*., 2000). In today's modern medicine, *Colchicum* tubers and seeds were used as a source of therapeutically active alkaloids called colchicinoids. Colchicine is the main alkaloid derivative obtained from all species included in the *Colchicum* genus (Ondra *et al*., 1995). In this review, information will be given about phylogenetic, chemical compounds, pharmacological and biological activity studies based on the results of phytochemical studies on *Colchicum* species.

1.2. Molecular, Biological and Content Lighting Studies

1.2.1. Phylogenetic Studies

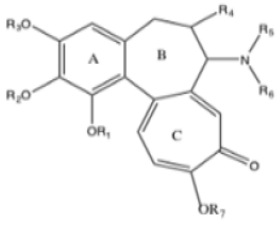
Turkey collected from 14 AFLP technology was used to examine the phylogenetic relationships between taxa *Colchicum*. A combination of 5 pairs of primers were used for this method. Later, NTSYS 2.1 software was used for statistical analysis of the data set. The phylogenetic tree was created using the neighbor-joining method and the maximum thrift method. These analyzes divided the samples into three main branches. These two analyzes have led to similar topologies. Similarly, 14 phylogenetic trees supporting taxonomy were formed through grouped main components. Using AFLP analysis, 14 taxa were evaluated using a combination of 5 primers. At the end of the study, 834 polymorphic bands were scored. The fit correlation coefficient between the data matrix and the fit matrix of the AFLP data was found to be 0.72. All participants based on molecular studies on genetic diversity, according to Turkey's other countries that have emerged, include more taxa (Metin *et al*., 2014). Sixteen *Colchicum* species and 37 different genetic variation patterns were evaluated using RAPD markers and trnL-trnF chloroplast DNA sequences together. At the end of the RAPD analysis, there were 861 polymorphic alleles containing an average of 33.88 ± 3.80 alleles for each primary gene, and also the mean frequency of the major alleles was found to be 0.067 ± 0.05. The sequence length of trnL-trnF varied between 1022 bp and 1081 bp. When the results were examined, it was seen that *Colchicum* species were grouped well because of RAPD analysis. These data were supported using PCA, structure analysis and haplotype network analysis. As a result of this study, it was revealed that this method is not sufficient to correctly distinguish and characterize the *Colchicum* genus (Tüyel *et al*., 2020). Phylogenetic analysis of 49 *Colchicum* species among 168 genotypes was performed using PCR-based markers. Using randomly amplified polymorphic DNA (RAPD), simple sequence repeat spacer region (ISSR), amplified fragment length polymorphism (AFLP) markers, 8459 alleles were identified. Besides genetic diversity analysis, principal component analysis (PCA) was also performed. As a result of PCA, it was seen that RAPD and ISSR markers can divide the population into 3 groups, AFLP markers can be divided into 5 groups, and there is no grouping because of morphological features. In this study, 4 different "neighbor-joining" clodograms were created with RAPD, AFLP and ISSR markers. Since similar results could not be found in this clodogram, a consensus clodogram covering all markers was created. This consensus showed that *C. serpentinum* Woronow ex Miscz. and *C. hirsutum* Stef. species are the furthest from each other in the branch diagram (Tüyel, 2015). Species and taxa of this kind in Turkey, non-coding regions of the chloroplast genome of the genus *Colchicum* have been copied by PCR and the transcribed region was sequenced in the "ABI 310 Genetic Analysis System". The ClustalW

program was used to compare the data obtained as a result of sequencing. The genotypes collected from these samples were determined by using STRUCTURE (v.2.3.) Software. The GenAlEx (v.6.41) program was used for principal component analysis (PCA) to reveal the genetic variation of the *Colchicum* genotype in the gene bank. For systematic evolution analysis, a neighbour-joining based genetic tree was created using the MEGA 6.06 program. STRUCTURE, PCA and phylogenetic analysis demonstrated large-scale agreement. Analysis divided the genotypes into two groups. The biggest difference between *C. kurdicum* (Bornm.) Stef. and *C. variegatum* L. populations were found to be 0.023 (Uncuoğlu, 2015). Phylogenetic analysis of ITS sequences of nuclear DNA *Colchicum* species of flora has been carried out in Turkey. They performed the sequence analysis in the "ABI 310 Genetic Analysis System". ClustalW program was used to compare the received sequence data. STRUCTURE (v.2.3.) software was used to determine the general structure and GenAlEx (v.6.41) program was used to reveal the variation of *Colchicum* haplotype in the gene pool. Then they performed principal component analysis (PCA). It has been found that this type of phylogenetic tree is fully consistent with the results of PCA and STRUCTURE analysis (Seren, 2015).

1.2.2. Phytochemical Studies

The compounds isolated as a result of phytochemical studies on *Colchicum* species and whose structures were illuminated were given by grouping. They used liquid chromatography-mass spectroscopy (LC-MS) and liquid chromatography-ultraviolet / visible photodiode array (LC-UV / Vis PDA) techniques as content analysis studies in *C. tauri* Siehe ex Stef., *C. stevenii* Kunth. and *C. tunicatum* Feinbrun species. With these techniques, they isolated 16 alkaloid compounds (Demecolcine, *N*-Methyl-(-)-demecolcine, 3-Dimethyl-*N*-methyl-(-)-Demecolcine, 2-Dimethyl-(-)-colchicine, Colchiciline, Colchifoline, Colchicine *β*-Lumi-(-)-colchicine, 3-Demethyl-(-)-demecolcine, 2-Dimethyl-(-)-demecolcine, 3-Dimethyl-(-)-colchicine, Apigenin, Isoandrocymbine, Crocifl orinone, *O*-Methyl-(-)-androcymbine, Cornigerine, Colchicine) from the underground and aboveground parts of the plants and made the structure determinations of these compounds (Gharaibeh et al., 2012). They determined the isolation and the concentration of alkaloid and colchicine (Colchicine, colchifoline, 2-demethylcolchicine, demecolcine, 4-hydroxycolchicine and N-deacetyl-N-formylcolchicine) from different parts of *C. chalcedonicum* Azn. and *C. micranthum* Boiss. species by the HPLC method. They investigated the phenolic compounds of each extract by the LC- MS / MS method. All *C. micranthum* extract has the highest amount of colchicine of all extracts. They showed that 19 phenolic compounds were present by the LC- MS/MS analysis method (Figure 1) (Gülsoy-Toplan *et al*., 2018).

Figure 1. Six compounds isolated from *C. chalcedonicum* and *C. micranthum*

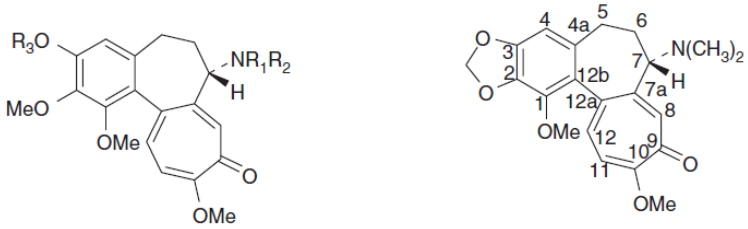


1: R_1: CH_3, R_2: CH_3, R_3: CH3, R4: H, R_5:H, R_6: $COCH_3$, R_7: CH_3
2: R_1: CH_3, R_2: CH_3, R_3: CH_3, R_4: H, R_5:H, R_6: $COCH_2OH$, R_7: CH_3
3: R_1: CH_3, R_2: H, R_3: CH_3, R_4: H, R_5:H, R_6: $COCH_3$, R_7: CH_3
4: R_1: CH_3, R_2: CH_3, R_3: CH_3, R_4: H, R_5:H, R_6: CHO, R_7: CH_3
5: R_1: CH_3, R_2: CH_3, R3: CH_3, R_4: OH, R_5:H, R_6: $COCH_3$, R_7: CH_3
6: R_1: CH_3, R_2: CH_3, R_3: CH_3, R_4: H, R_5:H, R_6: CH_3, R_7: CH_3

They identified bioactive compounds of underground and surface extracts of *C. autumnale* L. species using GC-MS and UHPLC-Q Exactive Orbitrap methods. As a result of phytochemical studies, they proved the existence of phenols, flavonoids, glycosides and terpenoids (Hailu *et al*., 2021). The content analysis of *C. crocifolium* Boiss. species was examined by combining LC-MS and LC - UV / Vis PDA methods. This dereplication strategy used UV / PDA spectra to classify compounds into one of four structural groups and combined

this with retention time-mass spectra and molecular weight to identify the compounds. This strategy uses 10 compounds known from four different structural groups ((-) -demecolcine, 2-dimethyl- (-) - colchicine or 3-dimethyl - (-) - colchicine, N-diacetyl - (-) - colchicine, (-) - colchiciline, (-) - colchicine, β-lumidemecolcine, 2-dimethyl-β-lumicolchicine or 3-dimethyl-β-lumicolchicine, N, N-dimethyl-N-diacetyl-β-lumicornigerine, (-) - isoandrocymbine and (-) - autumnaline) was applied on a small amount of *C. crocifolium* extract to copy. In addition, a new compound, N, N-dimethyl-N-diacetyl - (-) - kornigerin has been identified (Alali *et al*., 2008). They analyzed using UV - VIS, FTIR and RAMAN spectroscopy to characterize the phytochemical compound determinations (polyphenols, tannins, flavonoids, terpenoids) of the hydroalcoholic extracts obtained from the underground and aboveground parts of the *C. autumnale* plant. As a result of the photosynthesis of the extracts, the presence of colchicine, polyphenols and flavonoids was confirmed by spectral studies (UV-VIS, FTIR and RAMAN) (Suica-Bunghez *et al*., 2017). The content of the *C. baytopiorum* C.D. Brickell species was studied for the first time. Nine known alkaloids have been isolated and determined the structures by spectral methods (UV, IR, 1H-NMR and ESI / MS). In addition, the presence of three alkaloids that could not be isolated from the plant was determined by LC / MS / MS spectrometry. Phenolic acids were detailed using LC / MS and 11 phenolic acids were detected (Pırıldar *et al*., 2010). It was analyzed using LC-MS and LC-PDA systems to amplify 10 known alkaloids from the *C. crocifolium* plant. This system screen information from one of the four main group of colchicinoids identified. A new colchicinoid has been identified as N, N-dimethyl-N-diacetyl- (-) - kornigerin and with four but known compounds new to this species ((-) - colchicine, (-) -demecolcine, (-) - N-methyl - (-) - deccolin and 3-dimethyl- N - methyl - (-) - dememoline) has been isolated together (Figure 2) (Alali *et al*., 2010).

Figure 2. *Colchicum crocifolium* Boiss. isolated compounds



1: R_1=H, R_2=$COCH_3$, R_3=CH_3
2: R_1=H, R_2=CH_3, R_3=CH_3
3: R_1=CH_3, R_2=CH_3, R_3=CH_3
4: R_1=CH_3, R_2=CH_3, R_3=H

5

Ultra-high performance liquid chromatography combined with quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS) of extracts from flower, tuber and leaf parts of *C. triphyllum* Kunze species, mainly including alkaloids, flavonoids, lignans, phenolic acids and tyrosol equivalents It has allowed the hypothetical explanation of 285 compounds while considering different matrix extracts. Of the most abundant polyphenols, flavonoids (119 compounds) were, while the isomers of colchicine, decolcin, and lumicolychicin were some of the most common alkaloids in every extract analyzed (Senizza *et al*., 2020). They determined the alkaloid content of the bulbs, leaves and seeds of *C. turcicum* Janka (3-dimethylcolchicine, colchipholine, N-diacetyl-N-formylcolchicine, colchicine, cornigerine, 2-dimethyldemecolcine, 3-dimethyldemecolcine, demetcholine) by the HPLC method. They found that onions also contain β-lumicolchicine, luteolin and vanillic acid (Husek *et al*., 1990). The phytochemical profiles (total tropolone alkaloids, total phenolic, total tannins, total flavonoids) of *C. speciosum* Steven, *C. robustum* (Bunge) Stef., *C. autumnale* species were determined using acidic potassium dichromate, Folin-Ciocalteu and aluminum chloride

methods. In addition, the HPLC method has been used for the identification and quantitation of tropolone alkaloids. They showed that the highest tropolone alkaloid, phenolic compound, tannin and flavonoid levels were in *C. autumnale, C. speciosum* and *C. robustum*, respectively. By HPLC analysis, they revealed the presence of colchicine, dimethyl colchicine, 2-dimethyl colchicine, 3-dimethyl colchicine, colchicoside, colchipholine, corniger and N-diacetyl-N-formyl colchicine in these *Colchicum* species (Davoodi *et al*., 2021). Phytochemical profiles of *C. kurdicum* species consisting of total tropolone alkaloid, total phenolic, total tannin and total flavonoid contents were determined by spectrophotometric method. They also analyzed tropolone alkaloid profiles by the HPLC method. In HPLC analysis, they determined that N-diacetyl-N-formyl colchicine, colchipholine, colchicoside and cornigerin were the most bioactive tropolone alkaloids (Azadbakht *et al*., 2020). The quantities of colchicine found in *C. stevenii* and *C. hierosolymitanum* Feibrun species were obtained using a simple TLC spectrophotometric method with an HPLC-UV method using gradient elution. They found the highest content of colchicine in *C. hierosolymitanum* bulbs, while *C. stevenii* leaves contain the highest amount of colchicine. As a source of colchicine, they found that the two strains investigated were at comparable levels to those found in *C. autumnale*, the traditional colchicine source (Alali *et al*., 2004). The determination of the content of *C. hierosolymitanum* in the onion part extracts of the species was carried out using a single quadrupole mass analyzer equipped with LC-MS, (+)-APCI ionizing interface. (-)-Colchicine (7) and eight (1-6, 8, 9) natural analogs have been identified and identified in the alkaloid-rich fraction. These compounds were first reported for the *C. hierosolymitanum* species (Alali & El-Alali., 2005). Biologically active components of *C. hierosolymitanum* and *C. tunicatum* were investigated. Five and four known colchicinoids were isolated (HPLC) and characterized (1D-NMR, low-resolution EI-MS and APCIMS) *from C. tunicatum* and *C. hierosolymitanum*, respectively. Colchicinoids from *C. tunicatum*; those obtained from (-)-colchicine, 3-dimethyl-(-)-colchicine, (-)-cornigerin, β-lumicolchicine, (-)-androbipheniline and *C. hierosolymitanum*; it has been reported as (-)-colchicine (I), 2-dimethyl-(-)-colchicine, (-)-kornigerini β lumicolchicine (Figure 3) (Alali *et al*., 2006).

Isolation (HPLC) and characterization (H-NMR) of active ingredients of *C. stevenii* resulted in the isolation of six cytotoxic compounds. For the first time of this type (-)-colchicine, 2-dimethyl-(-)-colchicine, (-)-cornigerin, β-lumicochicine, (-)-isoandrocymbine and (-)-O-methylenedrochimbin compounds have been reported (Figure 4) (Al-Mahmoud *et al*., 2006). Nine alkaloids (3-demethylcolchicine, 2-demethylcolchicine, colchifoline, N-diacetyl-N-formylcolchicine, colchicine, cornigerine, 2-dimethyldemecolcine, 3-dimethyldemecolcine) were isolated from 7 *Colchicum* species using a high performance liquid chromatographic method. They determined the compound containing 20 phenolics from 5 *Colchicum* species. Colchicum's major alkaloid is colchicine. All parts of *Colchicum* species were shown to contain colchicine, but seeds and bulbs contained more colchicine than other plant parts (Ondra *et al*., 1995). Comprehensive (poly)-phenolic and alkaloid profiles of flower, tuber and leaf extracts (methanol, water) obtained from *C. szovitsii* Fisch. & C. A. Mey. following different extraction methods were made. In this context, ultra-high performance liquid chromatography methods combined with UHPLC-QTOF-MS (quadrupole time-of-flight mass spectrometry) were carried out. The 195 polyphenols and 87 alkaloids were described hypothetically. While the most abundant polyphenols were flavonoids (83 compounds), colchicine and 2-dimethylcolchicine were some of the most common alkaloids in every extract analyzed. It has been stated that leaf extracts are a rich source in terms of total polyphenols and total alkaloids (Rocchetti *et al*., 2019).

Figure 3. Compounds isolated from *C. tunicatum* and *C. hierosolymitanum*

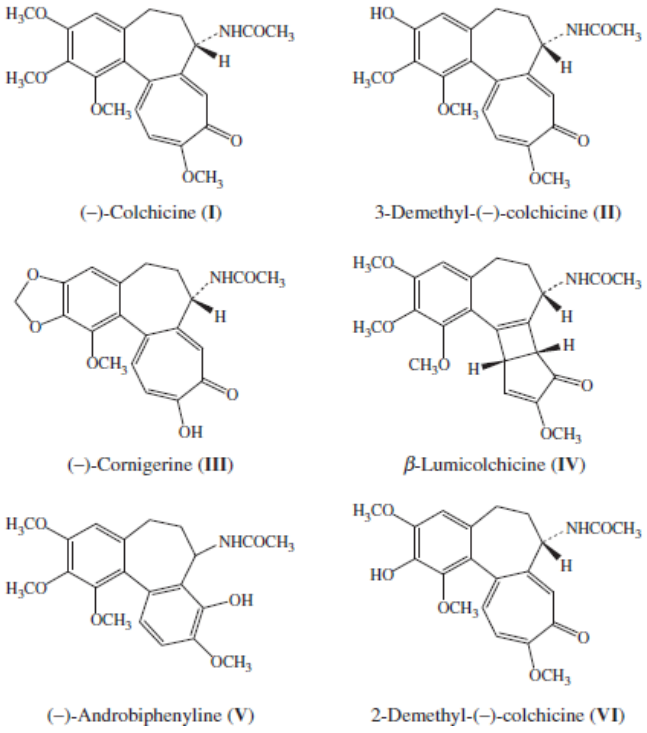
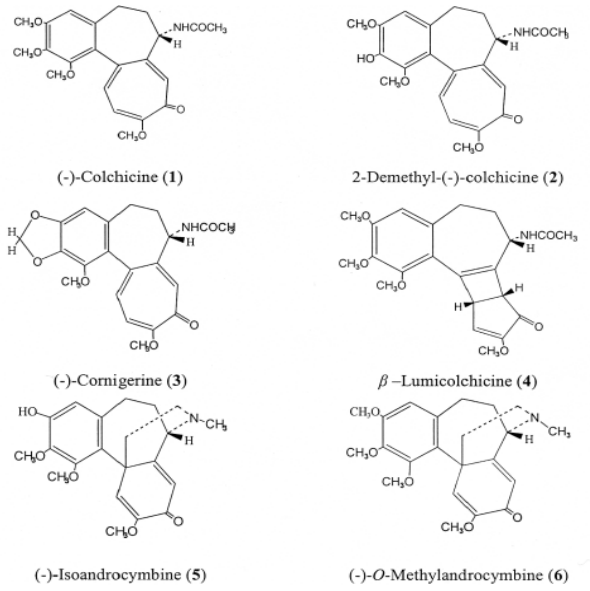


Figure 4. *Colchicum stevenii* Kunth isolated compounds



1.2.3. Antioxidant Activity Studies

In this regard, DPPH free radical scavenging activity of methanol extracts obtained from bulbs and seeds of plants was investigated in a study conducted on many *Colchicum* taxa. They reported that all extracts have a DPPH scavenging effect below 40% (Sevim *et al.*, 2010). DPPH, hydrogen peroxide, NO scavenging activities, metal chelating activity and total flavonoid and total phenolic amounts were investigated from methanol extracts obtained from flower parts of *C. speciosum* species. It has been determined that the plant has an antioxidant

effect (Ebrahimzadeh *et al*., 2010). DPPH and metal chelating activity on water and acetone extracts of *C. turcicum* species; their total phenolic content was examined. At the same concentrations, 53% inhibition of water extract and 48% inhibition of acetone extract were reported. Also, total phenolic contents of water and acetone extracts were determined as equivalent. (Kılıç *et al*., 2014). Antioxidant activity of underground and aboveground methanol, acetone, gasoline and ethanol extracts of *C. balansae* Planch. was determined by DPPH and ß-carotene methods. As a result of the β-carotene experiment, the highest antioxidant activity was observed in aboveground ethanol extracts and the least antioxidant activity in underground gasoline extracts. When DPPH free radical scavenging activity was examined, it was found that the highest effect was in underground gasoline extract, while the lowest activity was in ethanol extracts (Mammadov *et al*., 2009). It was determined by DPPH, ferric thiocyanate and thiobarbituric acid methods that methanol extracts of *C. sanguicolle* K. Perss. species showed weak antioxidant activity (Karagöz *et al*., 2015). The DPPH free radical scavenging activity of the methanol extract obtained from the tuber and stem of *C. speciosum* Scavenger activity was determined as 24.63 (Souri *et al*., 2008). FRAP and CUPRAC experiments were carried out in the water and methanol extracts obtained from flowers, leaves and tubers of *C. triphyllum* species by different methods. Leaf extracts showed strong antioxidant activity in terms of CUPRAC and FRAP reducing power (Senizza *et al*., 2020). Antioxidant activities of methanol and water extracts obtained from flowers, leaves and tubers of *C. szovitsii* were determined by FRAP, DPPH, CUPRAC, ABTS, phosphomolybdenum and metal chelation methods. Methanolic leaf extracts showed the highest ferric reducing antioxidant power (FRAP) reducing power and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (Rocchetti *et al*., 2019). Free radical scavenging activities of methanol extracts obtained from *C. autumnale* tubers and flowers were determined by the DPPH method. It was observed that the inhibition values of the extract obtained from the flower (52.81%) were higher than the extract obtained from the tuber (34.60%) (Suica-Bunghez *et al*., 2017). In another study on *C. autumnale*, the antioxidant activity of extracts prepared with different solvents (n-hexane, dichloromethane, methanol) was investigated by DPPH and ABTS methods. It was observed that dichloromethane extracts showed the most activity in both methods (Hailu *et al*., 2021).

1.2.4. Antioxidant Enzyme Inhibitory Activity Studies

In a study conducted on many *Colchicum* taxa, the cholinesterase inhibitory activities of methanol extracts obtained from the bulbs and seeds of plants against acetylcholinesterase (AChE) and butynylcholinesterase (BChE) were investigated. The Only moderate activity of the methanolic extract of *C. variegatum* (35.50 + 2.26 %) was detected against acetylcholinesterase. *C. crocifolium* and *C. variegatum* extracts showed significant antioxidant enzyme inhibitory activity against butynylcholinesterase (Sevim *et al*., 2010). In a study conducted on *C. triphyllum*, antioxidant enzyme inhibitory activities of methanol and water extracts obtained from flowers, leaves and tubers were determined. While the methanol extract obtained by maceration was active against tyrosinase in terms of inhibition, it showed moderate inhibitory activities against AChE and α-amylase (Senizza *et al*., 2020). Antioxidant enzyme inhibitory activities of methanol and water extracts obtained from *C. szovitsii* were determined. Methanolic extract is more active in enzymatic inhibition against tyrosinase, glucosidase, and acetylcholinesterase (AChE) than water extracts (Rocchetti *et al*., 2019).

1.2.5. Antimicrobial Activity Studies

As a result of antibacterial studies on ethanol extracts of *C. balansae* species, they have shown that it has a weak effect against many bacterial strains (*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). They determined that the *Staphylococcus aureus* ATCC 25923 bacterial strain was more sensitive to ethanol extract. When their antimicrobial activity was compared with control antibiotics, they showed that ethanol extracts had lower antimicrobial activity (Mammadov *et al*., 2009). Antimicrobial activities (*Micrococcus luteus, Mycobacterium smegmatis, Saccharomyces cerevisiae, Aspergillus niger*) of 9 compounds isolated from *C. brachyphyllum* Boiss. & Hausskn. species were investigated. None of the isolated compounds showed any activity (Alali *et al*., 2005). Turker and Usta (2008) investigated the antimicrobial (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Staphylococcus epidermidis*) activity of the fresh extract of *C. szovitsii*. While the fresh extract showed low activity (7.7 ± 0.2l mm) against *S. aureus*, it did not show any activity against other bacteria. The antimicrobial activities of *C. luteum* Baker methanol extract and its different fractions against *Escherichia coli, Bacillus subtilis, Klebsiella pneumonae, Shigella flexenari, Staphylococcus aureus* and *Salmonella typhi* bacteria were investigated. The Methanol extract (58 %) showed the highest activity against *Bacillus subtilis* (Ahmad *et al*., 2006).

1.2.6. Cytotoxic and Anti-inflammatory Activity Studies

Anti-inflammatory activities of extracts obtained from *C. autumnale* were investigated. Insertion analysis revealed that colchicoside (3 dimethyl colchicine glucoside) inhibited IL-6 having a binding energy of -7.1 kcal / mol with an RMSD value of 0.00 (Hailu *et al*., 2021). The cytotoxic effects of pure (PC) and chitosan-loaded (CCNPs) forms of colchicine isolated from *C. autumnale* on different cancer cell lines (HeLa, SKOV3, MDAMB231, Panc-1, PC3) were investigated. When looking at IC_{50} values, they are both effective against HeLa and SKOV3 cell lines. It has been found that their cytotoxic activities are weak against MDAMB231, Panc-1 and PC3 cell lines (Uddin *et al*., 2019). Another study investigated the cytotoxic effect of different concentrations of colchicine isolated from *C. autumnale* on the MCF-7 human breast adenocarcinoma cell line. It inhibited MCF-7 viability at concentrations of 10 and 100 µg/mL (Bakar-Ateş *et al*., 2018). In a study, the effect of colchicine isolated from *C. autumnale* on gastric carcinoma (AGS, NCI-N87) was investigated. It has been determined that it inhibits the proliferation of AGS and NCI-N78 cell lines depending on the dose. It promotes apoptosis of NCI-N87 cells. The *in vivo* experiment confirms that colchicine administration significantly suppresses tumor growth in mice through the induction of apoptosis at different concentrations (0.05 and 0.1 mg / kg) (Zhang *et al*., 2019). The cytotoxic effects of colchicine isolated from *C. autumnale* on HT-29 cell lines were investigated. They determined that the vitality of the cells decreased depending on the dose. Early apoptosis has been reported when cells are treated with 1 µg / mL colchicine (Huang *et al*., 2015). *C. baytopiorum* contains colchicine and its derivatives. The effects on the viability of the HeLa cell line were investigated. It was determined that both apoptotic and autophagic regulatory gene expressions increased significantly in the treatment group compared to the control group. It has also been reported to induce the crosslink between apoptotic and autophagic cell death in HeLa cells (Özsöylemez *et al*., 2016). The cytotoxic activity of 9 compounds isolated from *C. brachyphyllum* species on cancer cell lines (MCF-7, H460, SF268, BST) was investigated. They showed general cytotoxicity against BST (Alali *et al*., 2005). Cytotoxic activities of ethanol extracts obtained from *C. pusillum* Sieber species were investigated. All concentrations of the extracts have toxic effects on Colo-320 cells. As a result of immunohistochemical staining in Colo-741 cells, β-catenin, LGR-5 and caspase-3 immunoreactivities significantly increased, while Wnt7a immunostaining intensity decreased. It has also been found that it significantly increases caspase-3 immunoreactivity, indicating that apoptotic pathways are triggered (Becer *et al*., 2019). All pure compounds, cell lines on *C. hierosolymitanum* and *C. tunicatum* species; MCF-7 human breast carcinoma, NCI-H460 human large cell lung carcinoma, and SF-268 human astrocytoma were evaluated for cytotoxicity against three human

cancers. Among the compounds defined between EC_{50} values, (-)-Colchicine (I) and (-)-cornigerin (III) was determined as the most bioactive compounds (Alali *et al*., 2006). It has been shown that colchicine extracted from plants of the *Colchicum* genus has different physiological effects in various variations. However, the effect of colchicine on cytosolic free Ca^{2+} levels and related physiology on human oral cancer cells is unknown. This study examined whether colchicine changed Ca^{2+} homeostasis. OC2 has been observed to cause cytotoxicity in human oral cancer cells (Sun *et al*., 2019). To determine the cytotoxic activity on extracts of all parts of the *C. baytopiorum* species, the toxicity of *Artemia salina* was tested. As a result of the test, the extracts showed significantly high cytotoxic activity (LC_{50}: >100–23.20 µg / mL). In addition, they determined the cytotoxic activity of the extracts with the colorimetric MTT test on the K562 and HL60 cell lines. Except for seed extracts, all methanol extracts showed more cytotoxic activity on HL60 cells than K562 cells (Pırıldar *et al*., 2010). Brine shrimp eggs (*A. salina*) were used to determine cytotoxicity in the *C. luteum* taxon methanol extract. The median lethal dose (LD_{50}) given on the shrimp was measured as 42.43 µg / mL, expressing significant cytotoxic activity. The toxic potential effect of *C. luteum* Baker's fractionation did not change much. Chloroform and n-butanol fractions expressed the same cytotoxicity with LD_{50}: 42.43 µg / mL. The ethyl acetate fraction decreased slightly to LD_{50} 43.30 µg / mL in case of cytotoxic propensity. The aqueous fraction showed the least cytotoxic activity with LD_{50} of 45.15 µg / mL in the test. (Khan *et al*., 2011).

1.2.7. Pharmacological Activity Studies

According to many researchers, acetylcholinesterase inhibitors are stated to be the most effective treatment method to treat Alzheimer's disease. In the treatment of this disease, drugs with these inhibitors are used. However, some of these drugs are suggested to have severe side effects such as diarrhea, fatigue, nausea, muscle cramps as well as gastrointestinal, cardiorespiratory, genitourinary and sleep disorders. For this reason, new acetylcholinesterase inhibitors with higher potency are sought that can be obtained naturally. *C. balansae* is a plant that may be suitable for this inhibitor (Chattipakorn *et al*., 2007; Dhivya *et al*., 2014). For over 45 years, *Colchicum* species have been studied and used for therapeutic purposes. Different types of this plant are also grown for use in the pharmaceutical industry today. Tropolone alkaloid content of the species; FMF is helpful for the treatment of diseases such as gout, amyloidosis, cirrhosis, Behçet's disease, psoriasis, Hodgkin's lymphoma, myeloid leukemia and skin cancers. Since the synthesis method of alkaloids from *Colchicum* species has not been found yet, colchicine and other alkaloids are extracted from the plant source (Toplan *et al*., 2016). *C. luteum* type is a rare, expensive, and very medicinal herb. The medicine obtained from this plant is called Suranjan Talkh. This drug: The presence of alkaloid colchicine, which is claimed to be effective in arthritis, gout, rheumatism, and is used as a carminative, laxative and aphrodisiac. It is also applied externally to relieve inflammation and pain. It is an effective drug that draws attention by defining its palliative, therapeutic and other uses (Ansari *et al*., 2020). Arthritis is one of the most common diseases in the world that affects hundreds of millions of people. Suranjan Shirin is an important Unani Medicine drug derived from *C. autumnale* and widely used in the treatment of arthritis. The onion of the *C. autumnale* species is mainly used to relieve pain and inflammation and is also used to treat acute gout and some gout infections. (Akhtar & Siddiqui, 2018). It is one of the main drugs derived from the Suranjan *Colchicum* species and used in the Unani Medical System for arthritis disease. According to the research, there are two types of the drug under the name of Suranjan; one is Suranjan Shirin from *C. autumnale* species and the other is Suranjan Talkh from *C. luteum* species. They can be confused because they are morphologically similar to each other. Therefore, the marker compound (total alkaloid content) was quantitatively determined to distinguish these species. High performance liquid chromatography (HPLC) has been applied for both drugs. Colchicine concentration was higher in Suranjan Talkh (0.21%) compared to

Suranjan Shirin (0.15%). Thus, a phytochemical concentration criterion, namely colchicine content, is presented to distinguish between Suranjan Shirin and Suranjan Talkh (Siddiqui *et al*., 2019). Colchicine is an antimitotic agent like vinca alkaloids because it binds to tubulins and disrupts microtubule polymerization. This is a known main mechanism of colchicine (Levy *et al*., 1991). In a study conducted on rats, colchicine was shown to reduce urine excretion of Tamm-Horsfall protein, altering its structure, thus preventing it from forming a complex with the Bence-Jones protein (Sanders, 1993). This condition causes acute kidney failure in myeloma patients. According to the data obtained, although colchicine administration was successful in mice, it was reported that there was no change in serum and urine levels of Tamm-Horsfall protein in healthy volunteers (Cairns *et al*., 1994). They administered colchicine and silymarin to rats with liver damage, respectively. Both compounds have been shown to exhibit similar hepatoprotective effects against chronic liver damage (Favari & Pérez-Alvarez, 1996). Colchicine was administered to rats with CCI4-induced cirrhosis for 12 months. A decrease in the formation of cirrhosis tissue was observed in all of these rats (Le Hello, 2000). Using colchicine in the treatment of Gout was approved in 1987. Compared to patients who received placebo, there was a significant decrease in complaints between 18-30 hours after administration in patients who were administered colchicine. While the complaints decreased within 24 hours, it was observed that each patient had diarrhea 24 hours ago. Colchicine has been reported to have fewer side effects than other anti-inflammatory drugs (Ahern *et al*., 1987). Patients with chronic gouty arthritis in allopurinol treatment were divided into two groups. One group received 0.6 mg colchicine twice a day, while the other group received a placebo for 3 months in a randomized double-blind study. A significant reduction in acute gout attack was observed in the first group, on both allopurinol and colchicine treatment. (Borstad *et al*., 2004). In this study, 2 groups of 10 FMF patients were administered orally 0.6 mg colchicine or placebo three times a day for 6 months. They used colchicine to suppress febrile attacks. While 59 attacks were observed in 9 patients who received a placebo treatment, this number was observed as only 2 patients with 5 attacks in patients who received colchicine treatment. These results are statistically significant ($p < 0.002$) and prove that colchicine administration is highly effective in preventing attacks (Goldstein & Schwabe, 1974). Colchicine has been suggested for the treatment of serositis in patients suffering from FMF disease. In this study, three hundred and fifty FMF patients younger than 16 years of age were treated with colchicine for 6-13 years. Based on the results of the treated patients, 64% had complete regression and 31% partial regression. Amyloidosis did not develop in the colchicine regimen and colchicine side effects (Zemer *et al*., 1991). The effect of colchicine in non-insulin-dependent diabetes mellitus (NIDDM) has been studied. They noted that when colchicine was given to NIDDM patients at a dose of 0.5 three times a day, it significantly reduced the level of fasting and postprandial glucose in the blood. This study showed that colchicine has antidiabetic properties (Das, 1993). They studied patients with chronic idiopathic constipation to determine whether colchicine could increase bowel movements. As a result of the colchicine doses given for certain periods, bowel movements, nausea, abdominal pain and bloating symptoms were observed in patients. Based on the data obtained, it was concluded that it could be an effective agent for treating constipation patients (Verne, 2003). Colchicine is widely used in Behçet's syndrome. Studies in men and women have been followed over a long period of time. As a result of these observations, it was seen that colchicine exhibits different effects according to gender, but it is effective for arthritis in both sexes. It has been stated that colchicine has a visible effect on genital lesions in female patients (Yurdakul *et al*., 2001). Twenty-two psoriatic arthritis patients were treated with colchicine at a dosage of 0.02 mg per kg per day for 2-4 months. As a result of this treatment, 8 out of 9 patients showed significant improvement (Wahba & Cohen, 1980).

4. CONCLUSION

Colchicum, 39 taxa of a large distribution area with a large majority in Turkey are endemic. There are many phylogenetic and biological activity studies on these taxa. Phytochemical, antioxidant, antioxidant enzyme inhibitor, anti-inflammatory, antimicrobial and cytotoxic activities have been demonstrated in various studies on extracts obtained from these plants with different solvents. the advanced studies that can be done on the therapeutic alkaloids they contain, it will contribute to the pure and effective use of the compounds in the plant. Studies on *Colchicum* species have shown that the plant contains dense alkaloids and colchicine is the main alkaloid obtained from all species. It is known that alkaloids have pain relief, antitumor, treatment of cardiovascular diseases, antimalarial and morphine properties. It was understood with the literature reviews that the species belonging to this genus should be examined and brought to the world of science in our country. With this review, it was concluded that *Colchicum* species are worth researching in terms of the compounds they contain and their pharmacological effects.

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