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Abstract

Plants produce and store many organic compounds like amino acids, proteins, carbohydrates, fats, and alkaloids, which are usually treated as secondary metabolites. Many alkaloids are biologically active for humans. For thousand years, extracts from plants containing alkaloids had medicinal use as drugs and they owe their powerful effects thanks to presence of alkaloids. Alkaloids have anti-inflammatory, antibacterial, analgesic, local anesthetic, hypnotic, psychotropic, antimitic, and antitumor activity. Nowadays, alkaloids from plants are still of great interest to organic chemists, pharmacologists, biologists, biochemists, and pharmacists. Plants of Liliaceae family contain colchicine as the main alkaloid, which has cytotoxic activity. Colchicine has limited pharmacological application because of its toxicity, but many derivatives have been synthesized and their cytotoxic activity and tubulin-binding properties have been tested. Many of the synthetic derivatives showed good cytotoxic activity.

**Keywords:** colchicine, colchinoids, plants containing colchicine alkaloids, cytotoxic compounds, cancer cell lines, cytotoxic activity

1. Introduction

One of the best known biologically active compounds from ancient times is colchicine (Figure 1), an alkaloid naturally occurring in Colchicum autumnale a plant of Liliaceae family and also in Gloriosa superba. In the past, extracts from these plants containing colchicine were useful in gout therapy and still are [1]. The anti-gout action of colchicine could be explained by its powerful spindle toxicity [2, 3]. Moreover, colchicine is a useful medicine in the treatment of familial Mediterranean fever (FMF), liver cirrhosis, chronic myelocytic leukemia, Behçet disease, chondrocalcinosis and other microcrystalline arthritis also more recently in cardiovascular diseases, Sweet’s syndrome, and hepatic disorders (HCC hepatocellular carcinoma) [4–12].
In 2009, the FDA approved colchicine for the treatment of gout and familial Mediterranean fever (FMF) [1]. Recent investigations utilizing large cohorts of gout patients who have been taking colchicine for years have demonstrated novel applications within oncology, immunology, cardiology, and dermatology [4, 13–16]. Some emerging dermatologic uses include the treatment of epidermolysis bullosa acquista, leukocytoclastic vasculitis, and aphthous stomatitis. Colchicine has also anti-inflammatory and anticancer properties. Colchicine has been proven to have a fairly narrow range of effectiveness as a chemotherapy agent though it is also occasionally used in veterinary medicine to treat cancers in some animals. Nowadays, colchicine is very useful as an antimitotic agent in cancer research involving cell culture [17]. Colchicine has limited medical usage because of its high toxicity [18]. Because of this reason, many attempts have been made to design, synthesize new colchicine derivative and to screen them as cytotoxic agents to search more biologically active/effective compounds with lower toxicity.

2. Cytotoxic colchinoids in plants

Colchicine 1 and related alkaloids were isolated from many plants of Liliaceae family. The Colchicum species are most known plants in which colchicine exists in majority and other colchicine-like derivatives are in minority. Unripe seeds of Colchicum plants were found to contain 40% less colchicine 1 than fully ripe one [19]. Colchicine occurs in all parts of Colchicum plants but especially in seeds and bulbs. One of the most known plants which contain colchicine 1 is meadow saffron (C. autumnale, Figure 2). The other plants of Colchicum sp. are: C. crocifolium, C. turicum, C. kesselvingii, C. luteum, C. byzantinum, C. crocifolium, C. szovitsii, C. soboliferum, and many more [20]. Beside 1 in these plants of Colchicum species also are present: 2-demethylcolchicine 2, 3-demethylcolchicine 3, demecolcine 4, 2-demethylcolchicine 5, 3-demethylcolchicine 6, N-methyl-demecolcine 7, 3-demethyl-N-methyl-demecolcine 8, N-formyl-N-deacetylcolchicine 9 [19], N-deacetylcolchicine 10, N-deacetylcoclicheine 11, and colchicine 12. Many of colchicine alkaloids exist in plants in glycoside form [21, 22]. Colchicine and its derivatives are also present in other plants like: Gloriosa superba, Merendera species (M. kurdica, M. sobolifera, M. vaddeana, M. robusta, and many more), Bulbocodium vernum, Androcymbium palaestinum, and Kreysigia multiflora [20, 23]. In Gloriosa superba plants were found

![Colchicine molecule](color version available on the online version)
alkaloids: 1, 2, 5, 6, 2,3-O-didemethylcolchicine 13, 2,3-O-didemethyl-N-deacetylcolchicine 14, and 2,3-O-didemethyl-N-formyl-N-deacetylcolchicine 15 [22]. More recently, a new colchicine glycoside, 3-O-demethylcolchicine-3-O-α-D-glucopyranoside 41 has been isolated from Gloriosa superba seeds [22]. Moreover, in plants extracts were also isolated photolysis products of colchicine like α-lumicolchicine, β-lumicolchicine, γ-lumicolchicine, and their 3-O-demethyl derivatives [24, 25].

3. Unusual chemical structure of colchinoids

Colchicine (1) is an alkaloid with unusual structure and has the whole family of structural relations. This alkaloid was isolated in 1820 by Pelletier and Caventou [26]. Although listed at this point, colchicines are biogenetically very close to the isoquinoline alkaloids. Colchicines possess exocyclic N-atoms [15]. Corrected structure of colchicine molecule with seven-membered C ring proposed Dewar in 1945 [27]. Colchicine possesses both one stereogenic center at C7 and chirality axis, since the two rings A and C are not positioned in coplanar fashion (atropisomerism). In naturally occurring (−)-αR,7S-colchicine, the two rings (A and C) are oriented in a clockwise manner [15].

4. Natural, semi-synthetic, and synthetic colchicines

Many naturally occurring colchicine alkaloids (some of them are listed in Figures 3 and 4) have been converted into semi-synthetic compounds and have been prepared as potential antitumor agents. Usually starting with colchicine 1 hundreds of semi-synthetic and synthetic colchicine derivatives have been synthesized [28–30].

Starting compound was 1,2-O-didemethylcolchicine 16 converted into 1,2,3-O-tridemethylcolchicine 17 [28–30], 1,2,3-O-tridemethyl-N-deacetylcolchicine 18 [28–30], 1,2,3-O-trideethyl-N-deacetyl-N-trifluoroacetylcolchicine 19 [28–30], and 1,2,3-O-tridemethyl-N-deace...
tyl-N-formyl(2,4,6-trihydroxyphenyl)colchicine \(20\) [28–30]. 1,2-didemethyl-N-deacetylcolchicine \(21\) was converted into: 1,2-didemethyl-N-deacetyl-N-(propene-2,3-diol)colchicine \(22\) [31] and 1,2-didemethyl-N-deacetyl-N-(propene-2,3-diacetyl)colchicine \(23\) [31]. Derivatives \(24\) with halogen substituent and with alkyl, aryl, or hydrogen at C-10 position have also been obtained [32]. 10-demetoxy-10-azido-colchicine \(26\) [33] and 10-demetoxy-10-amino-colchicine = colchicineamid \(27\) [34]. 2-Demethyl-N-benzyldecolcincol = specicolchicine \(28\) [35] has been prepared from 2-demethyldecolcine. 10-O-p-tosylsulfonylcolchicine \(29\) can be converted into compound \(24\) [36]. One of the interesting derivatives modified at C-7 position by –sulfur-containing substitut is N-deacetyl-N-(2merkaptoacetyl)colchicine \(30\) (DAMA-colchicine) [37]. Glycopeptide dendrimer conjugates of colchicine modified at C-7 have been synthesized and tested as mitosis inhibitors [38]. N-substituted derivatives colchicine-lipids with different length of alkyl chain of oleny and stearyl groups have been obtained and their interaction with lipid membrane has been studied [39]. Ring-C-modified colchicine analogs with different nitroso substituents in Diels-Alder reaction have been obtained [40]. 3-Demethyl derivative of colchicine and 10-methylthicolchicine have been obtained also by regioselective bioconversion of \(1\) and \(31\) by microorganisms Bacillus INB-375 and stain of Bacillus megaterium ACBT03 [41, 42].

Figure 3. Naturally occurring colchicine derivatives (color version available on the online version).

Figure 4. Natural, seminatural and synthetic colchicines (chosen examples).
4.1. C-10 sulfur-containing derivatives

After many years of searching colchicine derivatives as good cytotoxic agents, it was established that exchange of methoxyl substituent –OCH₃ at C-10 position to amino group (NH₂, NHR₁, or NR₁R₂) and especially to methylthio (CH₃S–) or alkylthio increases cytotoxic activity. Thiocolchicine 31 is a colchicine 1 derivative used in the therapy of some diseases [43] and extensively studied in the field of oncological research as antimitotic agent [44–46]. There were mentioned some of wide range of synthesized colchicine compounds with thio substituent at C-10 position during last 60 years. Derivatives with alkylthio substituent at C-10 position have been synthesized from colchicine 31–35 (Figure 5) [47]. N-deacetyl-10-methylthiocolchicine 36 was converted into compounds: 37 [44], 38 and 39 [44]. 10-Methylthiocolchicin was modified at C-3 position to compound 3-demethoxy-3-amino-10-methylthiocolchicine 40 and then to 3-demethoxy-3-glycosylaminothiocolchicines 41–47 (Figure 5) [48]. From derivatives 48–52...
esters of 1-O-demethyl, 2-O-demethyl and 3-O-demethylthiocolchicine were also obtained 53–57 (Figure 5) [49]. 10-methylthiocolchicine has been demethylated to 1-demethyl-10-methylthiocolchicine 58, 2-demethyl-10-methylthiocolchicine 59, and 1,2-O-didemethylthiocolchicine 52 then 58 and 59 have been oxidized to quinine (Figure 6) [50]. Complex ethers of 3-demethyl-10-methylthiocolchicine 62–65 have been prepared as potential pharmaceuticals [51]. The C-7 amide group of ring B with (R)-configuration [15] is also one of the crucial factors which decide of molecule’s anticancer activity. Eight synthetic derivatives of N-deacetylthiocolchicine have been obtained and tested against cancer cell lines and 3 of them showed good activity 66, 67, 68 [52]. Thiocolchicine derivative 69 has been modified at C-2 carbon atom and then converted into salt 70 [53]. Among 37 thiocolchicine derivatives tested, compound 71 showed good activity as inhibitor of topoisomerases in vitro [54]. N-substituted thiocolchicine derivatives and their water-soluble phosphate salts 72–78 (and 5 others) have been obtained and their activity have been tested against cancer cell lines [55] (Figure 7).

Figure 6. Thiocolchicines with modified ring A: 60 1,4-quinone and 61 quinomethane.

Figure 7. Thiocolchicines modified on ring B.
From compound 79 acetamido –NHCOCH$_3$ substituent from C-7 has been removed and replaced by =CH$_2$ group [56]. Hybrids of vindoline, anhydrovinblastine, and vinorelbine with thiocolchicine 31 podophyllotoxin and baccatinIII have been tested in arresting cell cycle and cytotoxic activity [57]. Series of thiocolchicine-podophyllotoxin conjugates have been obtained and their tubulin activity has been tested [58].

Compounds 80, 81, 82, 83, 84, and 85 have been synthesized by four synthesis steps from colchicine 1 to thiocolchicine 31 then to 7-deacetylthiocolcicine 36 which has been converted into 80 and then to 81, 82, 83, 84, 85 and eight others which possess six-membered ring B [59].

5. Bioactivity of colchicine and its derivatives

Colchicine 1 has been known and used from ancient times, despite its toxicity to cure acute gout attacks because of its anti-inflammatory properties. After administration of colchicine 1, it is mainly metabolized in liver via demethylation by cytochrome P450 system (isoform CYP 3A4) to 2-demethylcolchicine 2 and 3-demethylcolchicine 3 [11]. Colchicine 12 was described as a metabolite in rats produced by cytochrome P450 3A4 isoform [60], but it does not occur in humans in vivo [61]. Colchicine’s most common toxicity is gastrointestinal (nausea, vomiting, diarrhea, abdominal pain) which occurs during first 24 hours after overdose. Toxic effect of colchicine appears after oral administration of 7–60 mg of colchicine and is fatal, symptoms occur in about 4 h and death in about 4 days. Severe colchicine overdose may be treated with a colchicine-specific antigen-binding immunoglobulin [11].

Beside colchicine 1 has many naturally occurring derivatives many attempts have been made to discover more effective and less toxic analogs by modifying the substituents of its basic structure.

Colchicine blocks mitosis metaphase due to different anti-mitotic effects: disruption of mitotic spindle formation and second disruption of the sol-gel formation. Colchicine can also interact with lipid membranes. The interaction between colchicine and membrane results with significant alternations of both the properties of the lipid membrane and alkaloid [39]. Tubulin is an α and β heterodimer initially identified as the cellular colchicine-tubulin protein [10, 62]. Colchicine can interact with human serum albumin, which has been studied by spectroscopic method [63, 64]. Study of colchicine-tubulin complex showed that colchicine binds at the location where it prevents curved tubulin from adopting a straight structure, which inhibits assembly. Microtubules are cytoskeletal polymers of tubulin involved in many cellular functions [65]. Their dynamic instability is controlled by many proteins and compounds such as colchicine.

Colchicine and its biologically active derivatives, especially thiocolchicine and its derivatives, have been extensively tested on cancer cell lines for in vitro cytotoxicity, in mice, evaluated for inhibition of tubulin polymerization [66], on axonal cytoskeleton of rat peroneus nerve [67]. Thiocolchicine has been studied as a potent compound to treat Peyronie’s disease [68]. Derivatives of thiocolchicine have been tested ex vivo to human T-lymphoblastoid (CEM) cells [69].
6. Cytotoxic activity of colchicine and its derivatives

Cytotoxic activity of colchicine has been known for many decades. In 1968, it was known that colchicine can efficiently bind to tubulin. Its antitumor activity derives from its tubulin binding activity [39]. Nowadays, it is known that colchicine can act with α and β tubulin in microtubules and disrupt the formation of microtubules. In past decades, many attempts have been made to design and synthesize new colchicine derivatives which could be less toxic and more effective compounds than colchicine as cytotoxic agents. On the basis of years of screening colchicine derivatives, their activity against human cancer cell lines structure: activity relationship has been established. It was found out that derivatives with alkylthio substituents at C-10 position and modified at C-7 usually are more active and less toxic than colchicine. One of the most known active semi-synthetic colchicine derivatives is thiocolchicine (10-methylthiocolchicine) 31. Some of the obtained derivatives seem to be effective and promising agents against selected human cancer cell lines and possibly in the future could be used as anticancer drugs. Cytotoxic activity of colchicine derivatives has been tested in in vitro experiments on mice (KLN205, A2C12, yB8, yD12, βD10, yA7, yA3, B3, βD5, A2B1, yD1) [70] or hamster (CHO-K1) [45] cancer cell lines and human cancer cell lines such as: MFC-7 human breast adenocarcinoma [40, 45, 47, 54, 71, 72] and MDA-MB-231 [47, 72] human Caucasian breast adenocarcinoma, SK-Br-3 human breast cancer cell line [46], DLD-1 [47] and LOVO [47] human colon adenocarcinoma, HCT-5 colon cancer, HCT-15 colon carcinoma [44, 45], A549 human lung adenocarcinoma [44, 52–55, 57, 58, 70], DMS-114 small lung cell cancer [44], SKOV-3 ovarian cancer [46], OVCAR-3 ovarian carcinoma [44], A2780 human ovarian carcinoma cell line [73], 1A9 human ovarian carcinoma [53], KB human epidermoid carcinoma [46, 53, 57], PC-3 prostate cancer [40], H460 human large cell lung carcinoma [71], SF268 human astrocytoma [71], HTC-8 human ileocecal carcinoma cell [46, 57], DU-145 human prostate carcinoma [46], SKMEL-2 human skin malignant melanoma [46, 54], SKMEL-5 human skin malignant melanoma [44], RXF-631 renal carcinoma [44], SNB-19 CNS carcinoma [44], RPMI-7951 malignant melanoma [56], TE671 human medulloblastoma [56], HepG2 human hepatocyte carcinoma [70], CaCo-2 human colon carcinoma [70], and CACK-1 kidney carcinoma [54]. As a positive control in cytotoxic tests were used: colchicine, doxorubicin or camptothecin and MTT tests [39, 57] or SRB tests MTS assay [70]. Values of IC_{50} for compounds 1, 4, 7, 8, 31, 32, 33, 34, and 35 are given in Table 1. Naturally occurring colchicine and other colchicine-like alkaloids were tested against human cancer cell lines and usually showed much better activity than parent compound.

Thiocolchicine 31 showed good activity against A2780 human ovarian carcinoma cell line with value of IC_{50} 1.6 nM [73]. The water-soluble compound 69 (salt of succinic acid of N,N-dimethyl-N-deacetylthiocolchicine) showed selective activity against HTC-8 0.022 μg/mL and SK-BR-3 0.012 0.022 μg/mL cancer cells [46]. The second salt of succinic acid of N-deacetylthiocolchicine 72 showed activity against five of tested cancer cell lines 0.001–0.005 μg/mL (HTC-8, SK-BR-3, A549, DU145, KB) [46].

Thiocolchicine derivative 83 modified at C-7 position showed good cytotoxic activity against A549, RPMI-7951, and TE671 cancer cell lines 0.001 nM/mL [56]. Derivatives 66, 67, and 68 showed good cytotoxic activity against A549, SKOV-3, SKMEL-2, HCT-15, and MCF-7 cancer cell lines with IC_{50} values 5.2–29.8 nM [52]. 69 and 70 showed significant activity against
tumor cell lines: A549, 1A9, and KB with values of IC₅₀ 0.02–0.06 μg/mL [53]. Hybrids of vincristine, anhydrovinblastine, and vinorelbine with thiocolchicine have been tested in arresting cell cycle and against A549 cell lines [57].

Many of tested colchicine derivatives and thiocolchicine derivatives obtained by partial synthesis were assayed measuring mitotic arrest in L1210 murine leukemia cell cultures [70], their binding to tubulin in vitro, their antitumor activity against the P388 lymphocytic leukemia screen in mice, and their inhibition of swelling produced in rat paws by injection with uric acid. To measure inhibition in binding different colchicine derivatives to tubulin, many tests have been used in vitro and in vivo: CD spectra [74], radiolabeled compounds, and cancer cell lines.

The effect on tubulin can be assessed in vitro by measuring inhibition of tubulin polymerization [53, 66, 70] and binding of radiolabeled colchicine to tubulin [75]. Significant inhibition in binding to tubulin greater than colchicine 1 was observed with 3-demethylcolchicine (3), 10-methylthiocolchicine 31, and 3-demethyl-10-methylthiocolchicine 48 [76]. Significant inhibition of binding radiolabeled colchicine to purified tubulin was observed with thiocolchicine and 3-demethylthiocolchicine (Table 2).

Colchicine showed to be too much toxic to be used as a drug candidate for cancer diseases. Colchicine is much more less toxic than colchicine [77]. Through past decades many derivatives were tested against cancer cell lines to checked their cytotoxic activity and activity in vitro to disrupt microtubule network and spindle formation. Binding of colchicine analogs to tubulin measured by competition for labeled colchicine is for 1 5 × 10⁻⁸, 31 4 × 10⁻⁸, and 41 2–3 × 10⁻⁵ [76]. Inhibition of tubulin assembly by thiocolchicine derivatives 69 and 70 is IC₅₀ 8.7 μM and IC₅₀ 3.8 μM, respectively [53]. The compounds 72, 76, and 77 showed potent inhib-

<table>
<thead>
<tr>
<th>Cell line compound</th>
<th>DLD-1</th>
<th>LoVo</th>
<th>MCF-7</th>
<th>MDA-MB-231</th>
<th>H460</th>
<th>SF268</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>43.0  [47]</td>
<td>118.8 [47]</td>
<td>41.3 [47]</td>
<td>25.3 [47]</td>
<td>32 [71]</td>
<td>25 [71]</td>
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<td>4</td>
<td>—</td>
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<td>52    [71]</td>
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<td>44 [71]</td>
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<td>7</td>
<td>—</td>
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<td>151 [71]</td>
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<td>8</td>
<td>—</td>
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<td>2440  [71]</td>
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<td>3200 [71]</td>
<td>981 [71]</td>
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<tr>
<td>34</td>
<td>177.3 [47]</td>
<td>149.6 [47]</td>
<td>564.2 [47]</td>
<td>1103.8 [47]</td>
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<tr>
<td>35</td>
<td>316.7 [47]</td>
<td>438.0 [47]</td>
<td>873.6 [47]</td>
<td>1773.3 [47]</td>
<td>—</td>
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<tr>
<td>Camptothecin</td>
<td>—</td>
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<td>0.309 [71]</td>
<td>—</td>
<td>0.024 [71]</td>
<td>0.043 [71]</td>
</tr>
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</table>

Table 1. The IC₅₀ values (nM) of compounds tested against cancer cell lines: MCF-7 [47], MDA-MB-231 [47], DLD-1 [47], LoVo [47], H460 [71] and SF268 [71]. Data were obtained from triplicate experiments. Doxorubicin was used as positive control (MTT test) [47].
bition of tubulin assembly IC\textsubscript{50} = 0.8–1.1 μM, for comparison for 1 is 1.5 μM \cite{54}. Compound 83 showed good inhibition of tubulin polymerization and inhibition of colchicine binding (%), IC\textsubscript{50} 3.4 μM and 60% and 79 IC\textsubscript{50} 2.4 μM and 91%; 82 IC\textsubscript{50} 6.6 μM and 78% \cite{56}. Hybrid thiocolchicine-vindoline causes cell cycle arrest in the G2/M phase \cite{57}. Inhibition of tubulin polymerization has been studied with thiocolchicine-podophyllotoxin conjugates, where 31 was modified at C-7 substituent \cite{63}.

\textit{In vivo} P388 mouse leukemia test data P388 for colchicine 1 is 0.5, 31 is 0.18, and 48 is 5 [mg/kg] \cite{76}.

### 7. Pharmacological use of colchinoids

#### 7.1. Colchicine prodrugs

Some of colchicines have been tested as prodrugs. Zyn-linked\textsuperscript{TM} colchicines which are conjugates of colchicine derivatives with proprietary lipophylic molecules (ZYN-160 4-formyl-thiocolchicine, PKH139, PKH153, PKH147) via acid cleavable linkages (PKH155, PKH159, ZYN-217) produced prodrugs (PKH140, PKH154, PKH156, PKH158, ZYN-162) with enhanced antitumor activity (A2780 human ovarian carcinoma cell line) \cite{73}. Conjugates have blocked cell in the G2/M phase of the cell cycle and were up to 100-fold less active in vitro than unlinked drug \cite{73}. Ring B-modified colchicine derivative CT20126 showed immunosuppressive and cytotoxic activity \cite{78}. N-acetylcocolchinol phosphate is a prodrug (ZD6126) derived from colchicine \cite{79}. Thiocolchicine dimers IDN5404 and IDN5676 have been tested as prodrugs active as inhibitor of Topo-I and without loss of the spindle poison properties \cite{80}. Colchitaxel is another active compound with cytotoxic activity which combines colchicine and paclitaxel \cite{81}.

#### 7.2. Drugs with colchicine

Besides antitumor activity, colchicine has anti-inflammatory properties. Colchicine reduces the formation of uric acid crystals in the affected joint and thereby reduces the amount of acute inflammation and pain. It also decreases the levels of uric acid in the blood or the amount that is excreted in the urine. More recently colchicine has been proposed as a potential drug in treatment for various conditions (except gout), what can open new way of its possible future application. Nowadays, colchicine is the useful drug in illnesses: familial Mediterranean fever (FMF),

\begin{table}
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\begin{tabular}{|c|c|c|}
\hline
Inhibitor added & Inhibitor:radio labeled colchicine (%) & \\
& 1:1 & 10:1 & \\
\hline
Non-radio-labeled 1 & 25 & 83 & \\
2 & 14 & 60 & \\
3 & 25 & 77 & \\
31 & 55 & 94 & \\
48 & 41 & 89 & \\
\hline
\end{tabular}
\caption{Inhibition [%] of binding radiolabeled colchicine to purified tubulin \cite{76}.}
\end{table}
liver cirrhosis, disk problems, Behçet syndrome, prevention of post-pericardial syndrome, primary biliary cirrhosis, hepatic cirrhosis, dermatitis herpetiformis, Paget’s disease of bone, pseudogout, and idiopathic pulmonary fibrosis.

Colchicine can be used to treat familial Mediterranean fever in children 4 years of age and older.

Colchicine is available as a tablet, capsule, and a gel. In tablet form, it is available in a generic 0.6 mg tablet and as Colcrys 0.6 mg tablet. It is available as a capsule in a generic form of 0.6 mg and as Mitigare 0.6 mg capsule. There is a topical gel form of Colchicum autumnale, available as ColciGel. Colchicine is commonly administered orally, and use of the topical gel is rare. Due to toxicity of colchicine from 2009, the injectable form is not available. Dosing is dependent on age of patient and kind of illness.

Usually, colchicine is a major component of tablets or capsules in which in a single tablet or capsule its amount is in range of 0.5 or 0.6 mg, sometimes is used as an injection (disk problems). Usually a man/woman of 60 kg takes a dose of 0.5–4.8 mg/day [82, 83]. Since 2008, only oral use of colchicine for patients is possible because of 50 cases of serious adverse events [84]. The known medicines with colchicine are: Colchicum Disper, Colcrys, Mitigare, and Colchimax. Col-Benemid or Proben-C is a drug where next to colchicine probenecid is added as uricosuric agent.

7.3. Drugs with colchicine derivatives

One of the known colchicine derivatives that has been used for the treatment of Hodgkin’s lymphoma and chronic granulocytic leukemia is N-deacetyl-N-methylcolchicine, brand name is Colcemid [72]. Moreover, its efficacy against melanoma and prostatic cancer has been established. Thiocolchicoside (=glucopyranosyl derivative of the semi-synthetic 3-O-demethylthiocolchicine 41), is well-known as a muscle relaxing agent and as an anti-inflammatory drug substance [85]. This compound is registered in different countries under the trade names of Colcamyl, Coltramyl, Coltrax, Mior, and Musco-Ril. Muscle spasm is one of the main factors responsible for chronic pain, and because this particular drug reduces muscle tone, it is used in therapy for the treatment of contractures and inflammatory conditions that affect the muscular system [48].

8. Docking studies

A new tool for searching new potent anticancer agents is docking studies. Some years ago it became possible to study new compounds of possible biological activity by new technical methods like molecular modeling and docking studies [37, 86–90].

9. Conclusion

The way to search new colchicine derivatives especially thiocolchicine derivatives seems to be worth trying because of its promising cytotoxicity. Many new derivatives have been obtained, have been tested for many different cancer cell lines, and many of them seem to be promising anticancer agents in the future.
Scientists still keep designing and synthesizing more and more colchicine derivatives for searching almost ideal anticancer agent. New methods, such as molecular modeling and docking studies, seem to be useful tool in searching for new colchicine derivatives as effective cytotoxic agents.

**Conflict of interest**

The author declares no conflict of interest.

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