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The influences of alkaloids of Chelidonium majus L., Colchicum autumnale L, Catharanthus roseus (L.) G.Don and Vinca minor L. on malignant neoplasms, the review of modern researches.

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Abstract: *natural alkaloids of Chelidonium majus L., Colchicum autumnale L. and Catharanthus roseus (L.) G.Don are anticancer agents. Some of them, such as colchicine, vincristine and vinblastine, are used in modern medicine, as chemotherapy medicines against malignant neoplasms, some of them are effective supplement to conventional methods or works to prevent cancer onset (chelidonine, sanguinarine, chelerythrine, protopine and allocryptopine). The effect of mitotic poisons that are alkaloids of Colchicum autumnale colchicine, Catharanthus roseus vincristine and vinblastine against malignant neoplasms began to be studied in the last century, the fact of mitotic spindle violation is given in a large number of works. However, the mechanisms of apoptosis under their influence have been little studied. The alkaloids of Chelidonium majus and Vinca minor L. have been much less studied, both in clinical studies and experimental ones, including insufficiently researched their anti-proliferative action, the ability to cause apoptosis and its possible mechanism. The research of apoptosis mechanisms caused by natural antitumor agents, will allow creating more effective and saving medicines based on the active ingredients of plant raw materials in the future. The aim of the paper was the analysis of the effect of the main alkaloids of Chelidonium majus, Colchicum autumnale, Catharanthus roseus and Vinca minor on malignant neoplasms and the mechanisms of such an influence with the help of analytic review of foreign and Ukrainian literature for the period 2002-2023 using medical database PubMed. The researched data obtained on cell lines, laboratory animals (in vitro) and clinic studies were analyzed. According to the analysis of the literature of recent years, the cytotoxic and anti-proliferative effects of natural alkaloids of Chelidonium majus chelidonine, Colchicum autumnale colchicine, Catharanthus roseus vincristine and vinblastine and Vinca minor vincamine on malignant neoplasms can be considered proven. Colchicine caused apoptosis in high doses, chelidonine, on the contrary, caused apoptosis of malignant cells in relatively low doses; in large doses it caused autophagy. The signaling pathways of apoptosis mechanisms of malignant cells under the influence of chelidonine, colchicine, vincristine, vinblastine and vincamine are much less studied and require additional research. Most of the results support the mitochondrial pathway, but there is a view in favor of the receptor-mediated pathway. The medicine, which contained alkaloids of Chelidonium majus,*

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showed a positive effect when used in combination with conventional antitumor therapy. Chelidonium majus and Vinca minor alkaloids are candidates for their use in antitumor therapy, but clinical studies of these agents are insufficient.

Keywords: Neoplasms, Colchicine, Vincamine, Vincristine, Vinblastine, Chelidonium majus, Chelidonine

Introduction

Malignant neoplasms are one of the most significant causes of death from diseases in the world (Dhyani, Quispe & Sharma, 2022; Sharifi-Rad, Quispe & Butnariu, 2021; Sharifi-Rad, Quispe & Patra, 2021).

Medicinal plants containing alkaloids are used in phytotherapy in different countries to prevent tumors onset (Dhyani et al, 2022; Gilca, Gaman & Panait, 2010; Hossain, Quispe & Saikat, 2022; Koklesova, Liskova & Samec, 2020) and with combination together with conventional therapies of neoplasms (Ernst & Schmidt, 2005; Gansauge, Ramadani & Pressmar, 2002; Gilca et al, 2010; Ковальчук, Гуля та Лучків, 2006). Colchicine, vincristine, vinblastine and their synthetic derivatives are medicines of modern chemotherapy.

Among the medical plants containing alkaloids, the most noteworthy are *Chelidonium majus* L, *Colchicum autumnal*e L, *Catharanthus roseus* (L.) G.Don and *Vinca minor* L. The effect of mitotic poisons that are alkaloids by *Colchicum autumnale* colchicine and *Catharanthus roseus* vincristine and vinblastine against malignant neoplasms began to be studied in the last century, the fact of mitotic spindle violation is given in a large number of works. However, the mechanisms of apoptosis under their influence have been little investigated. The alkaloids of *Chelidonium majus* and *Vinca minor* have been much less studied, both in clinical studies and experimental ones, including insufficiently researched their anti-proliferative action, the ability to cause apoptosis and its possible mechanism.

The research of apoptosis mechanisms caused by natural antitumor agents, will allow creating more effective and saving medicines based on the active ingredients of plant raw materials in the future.

Aim

To analyze the influence of the chelidonine, sanguinarine, chelerythrine, protopine and allocryptopine contained in *Chelidonium majus*; colchicine contained in *Colchicum autumnale*; vincristine and vinblastine contained in *Catharanthus roseus*; vincamine contained in *Vinca minor* on malignant neoplasms and the mechanisms of these agents` effects reflected in modern scientific literature.

Materials and methods

Analytical review of Ukrainian and foreign literature for the period 2002-2023, which is dedicated to the effect of *Chelidonium majus, Colchicum autumnale, Catharanthus roseus, Vinca minor* and/or their main alkaloids on malignant neoplasms and the mechanisms of such an influence with the help of medical database PubMed.

Review and discussion

Greater celandine (*Chelidonium majus* L.), Papaveraceae Family. Celandine herb contains three main subgroups of isoquinoline alkaloids: with protoberberine (berberine, coptisine), protopine (protopine, allocryptopine) and benzophenanthridine (chelidonine, chelerythrine, sanguinarine) structures. Alkaloids in celandine exist both in the free and in the chelidonic acid-bound state. There are also flavonoids, ascorbic acid, carotenoids, organic acids and other biologically active substances in small quantities (Дашутіна, 2003). Among all

celandinealkaloids,themostbiologicallyactive are isoquinoline alkaloids, benzophenanthridine subgroup and especially, chelidonine, is the most effective (Havelek, Seifrtova & Kralovec 2016; Noureini & Esmaili, 2014).

According to Habermehl, Kammerer & Handrick, (2006) drug Ukrain, which included alkaloids of *Chelidonium majus* chelidonine, sanguinarine, chelerithrine, protopine and allocryptopine, is an inducer of malignant cells apoptosis. The drug caused depolarization of the mitochondrial membrane and caspases activation. This process is shown in Figure 1.

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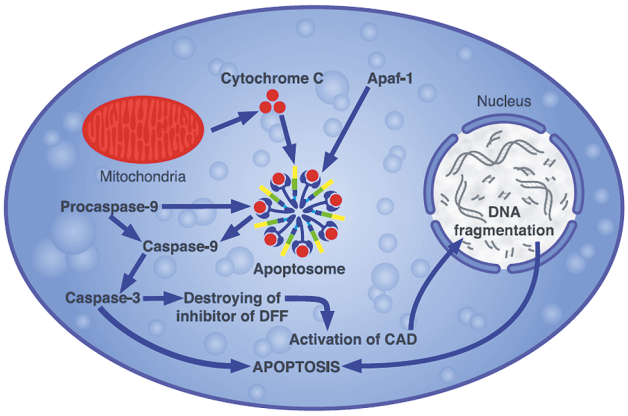

Figure 1. The probable scheme of malignant cells apoptosis under celandine alkaloids with the participation of intrinsic (mitochondrial) pathway. Depolarization of mitochondrial membrane causes cytochrome C releasing from mitochondria, which, together with Apaf-1 (Apoptotic peptidase activating factor 1) and procaspase -9 form apoptosome. Apoptosome activates caspase-9. the last can also be activated by procaspase-9. Activated caspase-9 activates caspase-3, which destroys inhibitor of DFF (DNA fragmentation factor). DFF activates CAD (caspase-activated DNase). CAD is an enzyme destroying DNA, which in turn leads to the final stage of apoptosis.

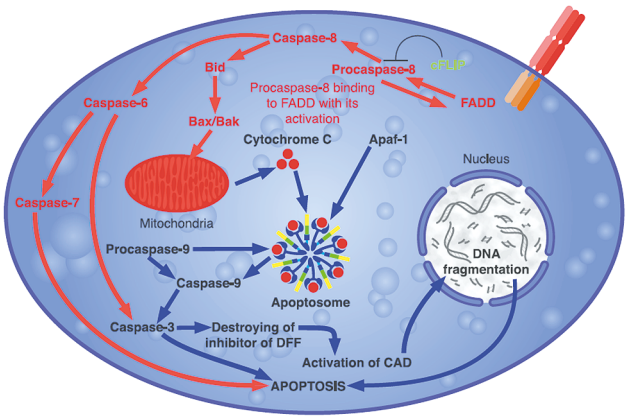

Figure 2. The probable scheme of malignant cells apoptosis under celandine alkaloids with the participation of extrinsic pathway and intrinsic (mitochondrial) pathways with the expression of procaspase-8 inhibitor and death receptors resistance. The expression of procaspase-8 inhibitor (FLIP, green color) causes the impossibility of caspase cascade activation from procaspase-8 to caspase-7. The same result takes place under death receptor resistance. The failed ways are shown with red. In spite of it, the apoptosis is possible. Apaf-1 -Apoptotic peptidase activating factor 1 DFF - DNA fragmentation factor) CAD -caspase-activated DNase)

Caspase-8 and FADD (Fas-associated Death Domain) are two important signaling molecules of the death receptors apoptosis pathway. It was reported that Ukrain-induced apoptosis did not require the presence of caspase-8 and FADD, expression of the caspase-8 inhibitor cFLIP-L (cFLIP – cellular FADD-like interleukin-1 converting enzyme (FLICE) inhibitory protein) or resistance to the death receptor ligands failed to inhibit Ukrain-induced apoptosis. This indicates a signaling pathway independent of the death receptor (Habermehl et al, 2006). At the same time, broad-spectrum caspase inhibitor zVAD-fmk blocked drug-induced cell death. The authors also noted the participation of Bcl-2 (B-cell lymphoma/leukemia-2), which are regulatory proteins exactly of mitochondrial pathway of apoptosis (Habermehl et al, 2006; Papaliagkas, Anogianaki & Anogianakis, 2007). Both pathways, extrinsic (death receptors) and intrinsic (mitochondrial) with the expression of caspase-8 inhibitor cFLIP and the resistance to death receptors are shown in the Figure 2.

The drug Ukrain, produced from Celandine, in combination with conventional antitumor treatment increased the survival of patients with pancreatic cancer (Gansauge et al, 2002). Its therapeutic effect on a number of malignant neoplasms is noted, while the methodological basis of most clinical studies was insufficient (Ernst & Schmidt 2005).

Among the alkaloids of *Chelidonium majus*, chelidonine is most studied. It induces apoptosis of cancer cells (Havelek, Seifrtova & Kralovec 2016; Noureini & Esmaili, 2014; Noureini & Wink, 2009; Paul, Bishayee & Ghosh, 2012; Камінський В.О., 2006;), including human lymphoma cells and works against this neoplasm together with other alkaloids, which are sanguinarine, chelerithrine and coptisine (Камінський В.О., 2006). Chelidonine also induces apoptosis of MCF-7 breast cancer cell line (MCF-Michigan Cancer Foundation, MCF-7 is breast adenocarcinoma cell line) (Noureini & Esmaili, 2014), HeLa cells (HeLa is cervical cancer cell line), (Paul et al, 2012), leukemic T-cells (Havelek et al, 2016), human ovarian cancer cells (Shen, Lee & Joo, 2022). Apoptosis is not the only way

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of chelidonine cytotoxic action, it is noted that chelidonine induces apoptosis at low doses in MCF-7 breast adenocarcinoma cells, but at high doses, it causes autophagy of this type of cancer cells (Noureini & Esmaili, 2014). There are studies of apoptosis`s mechanisms caused by chelidonine alone. Камінськiй (2006) notes that the induction of apoptosis was carried out at mitochondrial level. The author also suggests that the induction of lymphoma cells apoptosis under the influence of chelidonine can be carried out with the involvement of caspase-9 and caspase-8, the last one takes part in receptor-mediated pathway of apoptosis (Камінський В.О., 2006). Caspases participate in two different pathways of apoptosis: extrinsic, mediated through death receptors and subsequent activation of caspase-8, and intrinsic, mitochondrial pathway through activation of caspase-9 (Wen, Lin & Liu 2012). At the same time, caspase-8, which is formed at extrinsic pathway, can also activate the intrinsic pathway through Bid (Bid is proapoptic BH3 domain bcl2), that is, through a proapoptic member of the protein family bcl-2. Moreover, there are ways for caspase-8 activation without death receptors (Wen et al, 2012). These apoptic ways are shown in Figure 3. Taking into consideration the most scientific data, we suggest these mechanisms are to be the most probable.

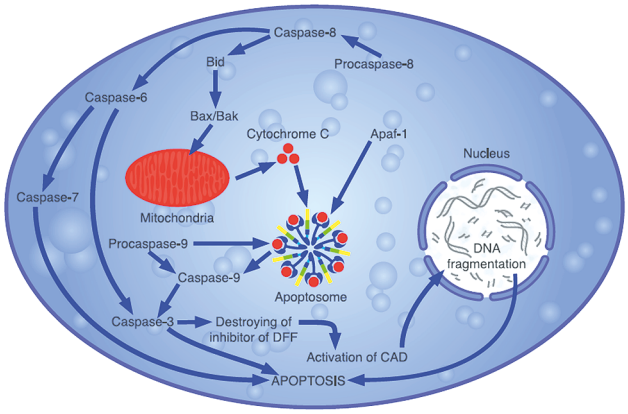

Figure 3. The probable scheme of malignant cells apoptosis under celandine alkaloids with the participation of extrinsic pathway and intrinsic (mitochondrial) pathways without death receptors participation. Apaf-1 -Apoptotic peptidase activating factor 1 DFF - DNA fragmentation factor) CAD -caspase-activated DNase) Bid, Bax, Bad - proapoptic proteins

The participation of both caspase-8 and caspase-9 is confirmed by Havelek et al (2016). Data by Камінський (2006) and Havelek et al (2016) partially contradict the data by Habermehl et al. (2006), who proved the insignificance of caspase-8 expression in apoptosis under the influence of drug Ukrain.

In favor of mitochondrial pathway of the effect of chelidonine, data on the disappearance of the mitochondrial membrane potential indicate (Havelek et al, 2016; Paul et al, 2012). Cell cycle arrest (Havelek et al, 2016; Noureini & Wink, 2009; Paul et al, 2012), DNA fragmentation (Paul et al, 2012) under the influence of chelidonine and inhibition of telomerase in submicromolar concentrations of chelidonine (Noureini & Esmaili, 2014) are also noted. These data support Noureini & Wink, (2009), who reported that low doses of chelidonine caused a decrease in telomerase activity.

The study of signaling pathways in HeLa cells showed that chelidonine could effectively induce apoptosis due to the expression of genes encoding p38, p53 and other proapoptic genes and suppressing the expression of Protein kinase B (AKT), phosphatidylinositol 3-kinases (PI3K), Janus kinase 3 (JAK3), signal transducer and activator of transcription 3 (STAT3), oncoproteins E6 and E7, and anti-apoptotic genes (Paul et al, 2012).

Autumn crocus (*Colchicum autumnale* L), Colchicaceae family. All parts of the plant contain alkaloids: colchicine and colchamine. Colchicine has significant anti-proliferative activity (Li, Hu & Pu, 2022), it inhibited sufficiently proliferation and induced apoptosis by modulating the expression level of several genes and carried out anticancer effect on human breast adenocarcinoma MCF-7 and mouse breast cancer cell line 4T1 (Adham Foumani, Irani & Shokoohinia, 2022). The authors suggest that colchicine may be a potential candidate for the prevention and treatment of breast cancer. A serious drawback of colchicine, which limits its use in effective doses, is toxicity (Lin, Yeh & Huang, 2021), however, a currently synthesized colchicine-magnolol hybrid inhibited the growth of lung carcinoma cells (Li et al, 2022). Colchicine works primarily by inhibiting microtubule polymerization (Dhyani et al, 2022),

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which in turn, affects numerous cellular processes, namely: maintenance of shape, signaling, division, migration, and cellular transport (Angelidis, Kotsialou & Kossyvakis, 2018). In addition to its effect on microtubule polymerization, which is anti-proliferative, colchicine also induces apoptosis. Chen et al, (2012) believe that apoptosis under the action of colchicine is carried out through the intrinsic, i.e. mitochondrial, pathway. A decrease of the mitochondrial membrane potential, activation of caspase-3 and -9, an increase of Bax (BCL2 associated X protein, apoptosis regulator) and a decrease of Bcl-2 were shown (Chen et al, 2012). According to these data, this mechanism is similar to the one shown in Figure 3 for celandine alkaloids.

Pink periwinkle (*Catharanthus roseus* (L.) G.Don), Apocynaceae Family

Pink periwinkle herb contains up to 60 alkaloids, several of them are important. *Catharanthus roseus* alkaloids were among the first plant alkaloids to be developed as anticancer drugs for humans. Currently, they are divided into the first generation drugs (vincristine, vinblastine), the second generation (semi-synthetic derivatives (vindesine) and the third generation ones (vinorelbine, vinflunine) (Arora & Menezes, 2021). They are mitotic poisons, specific antitubulin remedies. Vinblastine is used as an antitumor chemotherapy drug (Haque, Rahman & Faizi, 2018), including in the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, breast cancer, Kaposi's sarcoma, prostate cancer, acute lymphoblastic leukemia and nephroblastoma (Dhyani et al, 2022), as well as in veterinary practice in the chemotherapeutic treatment of mastocytoma in dogs (Macedo, de Queiroz & Casagrande, 2022; Ossowska, Picornell & Finotello 2023; Stiborova, Treggiari & Amores-Fuster, 2019; Todd, Nguyen & White, 2021).

Vincristine is used as a chemotherapy remedy in the treatment of leukemia, lymphoma, myeloma, breast cancer (Dhyani et al, 2022), especially non-Hodgkin lymphoma (Škubník, Pavlíčková & Ruml, 2021).

The mechanism of pink periwinkle alkaloids is the following: inhibition of tubulin polymerization in low doses, tubulin polymerization is necessary for the formation of the mitotic spindle during the metaphase of the cell cycle; in high doses, pink periwinkle alkaloids cause cell cycle arrest and apoptosis. (Arora & Menezes, 2021). The mechanism of action on microtubules is similar to that of colchicine, with tubulin having three binding domains: paclitaxel, *Catharanthus roseus* alkaloids and colchicine domains. (Cheng & Feng (2020)

Small periwinkle (*Vinca minor* L.), Apocynaceae Family

Vincamine, an alkaloid of *Vinca minor*, is used as a dietary supplement and vasodilator. Al-Rashed, Baker & Ahmadl, (2021) have demonstrated for the first time the possibility of using vincamine as an antitumor agent on the adenocarcinoma cell line A549 of human alveolar basal cell epithelium. Vincamine stimulated caspase-3-dependened apoptosis and reduced mitochondrial membrane potential, stimulated the release of cytochrome C. The non-toxicity of vincamine was shown on non-tumorigenic cell lines - BEAS-2B (human bronchial epithelial cell line) and 3T3-L1 (cloned cell line from a mouse embryo) (Al-Rashed et al, 2021). The release of cytochrome C and decreased mitochondrial membrane potential, which were researched by Al-Rashed et al. (2021), are indicators of the intrinsic signaling pathway of apoptosis. This way is shown in Figure 1. It is significant that one study proved the apoptosis of malignant cells and the absence of toxicity of the drug for healthy cells.

Conclusions

According to the analysis of the literature of recent years, the cytotoxic and anti-proliferative effects of natural alkaloids of *Chelidonium majus* chelidonine, *Colchicum autumnale* colchicine, *Catharanthus roseus* vincristine and vinblastine and *Vinca minor* vincamine on malignant cells can be considered proven.

Colchicine caused apoptosis in high doses, chelidonine, on the contrary, caused apoptosis of malignant cells in relatively low doses; in large doses it caused autophagy.

The signaling pathways of apoptosis mechanisms of malignant cells under the influence of chelidonine, colchicine, vincristine, vinblastine and vincamine are much less studied and require additional research. Most of the results support the mitochondrial pathway, but there is a view in favor of the receptor-mediated pathway.

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The medicine, which contained alkaloids of *Chelidonium majus*, showed a positive effect when used in combination with conventional antitumor therapy.

Chelidonium majus and *Vinca minor* alkaloids are candidates for their use in antitumor therapy, but clinical studies of these agents are insufficient.

Financing

This study did not receive external funding

Conflict of interests

The authors declare the absence of any conflict of interests

Consent to publication

All authors have read the text of the manuscript and have given their consent for its publication

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Вплив алкалоїдів Чистотілу великого, Пізньоцвіту осіннього, Барвінку рожевого та Барвінку малого на злоякісні новоутворення, огляд сучасних досліджень

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Анотація: *природні алкалоїди Чистотілу великого, Пізньоцвіту осіннього та Барвінку рожевого є протипухлинними засобами, які використовуються у сучасній медицині як препарати хіміотерапії злоякісних новоутворень (колхіцин, вінкристин, вінбластин), іноді як ефективне доповнення до конвенційних методів лікування та як засоби, що попереджають виникнення новоутворень (хелідонін, сангвінарин, хелеритрин, протопін та алокриптопін). Вплив «мітозних отрут», алкалоїдів Пізньоцвіту осіннього колхіцину, Барвінку рожевого вінкристину та вінбластину на злоякісні новоутворення почав вивчатися ще у минулому столітті, факт порушення мітотичного веретена наведений у великій кількості робіт, проте механізми апоптозу під їх впливом вивчені мало. Ще набагато менш вивчені алкалоїди Чистотілу великого та Барвінку малого, як у клінічних дослідженнях, так і експериментальних, у тому числі недостатньо досліджені антипроліферативна дія, здатність викликати апоптоз та його можливі механізми. Дослідження механізмів апоптозу, що спричинений природними протипухлинними засобами, дозволить у майбутньому створити більш ефективні та безпечні лікарські препарати на основі діючих речовин рослинної сировини. Метою дослідження був аналіз впливу головних алкалоїдів Chelidonium majus L, Colchicum autumnale L, Catharanthus roseus (L.) G.Don та Vinca minor L. на злоякісні новоутворення та механізми такого впливу, за допомогою аналітичного огляду української та іноземної літератури, здійсненого за допомогою медичної наукової бази PubMed за 2002-2023 роки. Аналізувалися дані досліджень на клітинних лініях, лабораторних тваринах (in vitro) та клінічні дослідження. Відповідно до огляду літератури останніх років можна вважати доведеним цитотоксичний та антипроліферативний вплив природних алкалоїдів Чистотілу великого (Chelidonium majus) хелідоніну, Пізньоцвіта осіннього (Colchicum autumnale) колхіцину, Барвінка рожевого (Catharanthus roseus) вінкристину, вінбластину та Барвінка малого (Vinca minor) вінкаміну на злоякісні клітини. Колхіцин викликав апоптоз у високих дозах, хелідонін навпаки, спричинював апоптоз злоякісних клітин у відносно низьких дозах, у великих викликав аутофагію. Сигнальні шляхи механізмів апоптозу злоякісних клітин під впливом хелідоніну, колхіцину, вінкристину, вінбластину та вінкаміну вивчені набагато менш та потребують додаткових досліджень, більшість результатів свідчить на користь мітохондріального (внутрішнього) шляху, але є точка зору на користь рецептор-опосередкованого шляху. Препарат, що містив алкалоїди Чистотілу великого, показав позитивну дію при комплексному застосуванні разом зі конвенційною протипухлинною терапією. Алкалоїди Барвінку малого вінкаміну та Чистотілу великого є кандидатами на їх використання у протипухлинної терапії, проте клінічні дослідження зазначених препаратів недостатні.*

Ключові слова: новоутворення, Чистотіл великий, хелідонін, колхіцин, вінкамін, вінкристин, вінбластин