Sanguinaria canadensis (Sanguinaria canadensis L.) Publication 2: biological action, use in traditional medicine and modern world medical and pharmaceutical practice

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Blood root (Sanguinaria canadensis L.). Article 2: biological activity, use in traditional medicine and current success in medical and pharmaceutical practice

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SUMMARY

An informational and analytical study of the spectrum of biological activity, the experience of traditional use and modern ideas about the prospects for the use of Canadian sanguinaria (Sanguinaria Canadensis L.) in modern medical and pharmaceutical practice has been carried out. It is shown that the accumulated ethnobotanical and ethnopharmacological material has led to significant interest in the experimental and clinical study of sanguinaria on the part of individual researchers and entire scientific teams.

Based on the analysis of published research results, the antitumor, anti-inflammatory, antimicrobial, antiviral, antiparasitic, antidiabetic effect of rhizome extracts and individual alkaloids isolated from this plant has been shown. The works were revealed that describe the mechanisms of action of sanguinarine and chelerythrine on a cancer cell, as well as processes that determine the antitumor effect of sanguinaria alkaloids, their effect on the activity of the stomach and intestines, heart and blood vessels, as well as on insulin resistance.

Thus, the study made it possible to establish that the rhizomes of sanguinaria can be a promising source of modern domestic medicines and / or phytonutrients for the creation of dietary supplements for food and specialized food products.

Key words: traditional medicine, Sanguinaria Canadensis L., bloody root, sanguinarine, sanguinaria, canadian sanguinaria, alkaloids, antitumor effect, antiviral effect, antimicrobial effect.

RESUME

This review presents analysis of biological activity, traditional medicine and current scientific data on use of blood root (Sanguinaria Canadensis L) in medical and pharmacological practices. It was shown that based on its successful use in traditional medicine for centuries, this herb generates significant interest from research laboratories across the globe. Based on the evaluation of the published material, this study provides the solid evidence that blood root and its specific alkaloids have anti-cancer, anti-inflammatory, anti-viral, anti-microbial, anti-parasitic, and anti-diabetic action.

The mechanism of action of active components of blood root, sanguinarine and chelerythrine, on cancer cells, their effect on the stomach, gastrointestinal tract, heart and vascular system as well as on resistance to insulin is discussed. In conclusion, the presented review established strong support that blood root is a promising component for modern pharmacological forms and food supplements for special medical conditions and / or prophylactics.

Keywords: traditional medicine, Sanguinaria Canadensis L., bloodroot, alkaloids, sanguinarine, antitumor effect, antiviral effect, antimicrobial effect.

INTRODUCTION

Taking into account the growing interest in herbal antiviral, antimicrobial, antifungal and anticancer drugs [1], we carried out an information-analytical study (reflected in two consecutive publications) of one of the plant sources to obtain drugs of the indicated spectrum of action - Sanguinaria canadensis L. According toforeign studies (including ethnobotanical and ethnopharmacological), Canadian sanguinaria has a long experience of traditional use and is considered a promising source of alkaloids, including antitumor, anti-inflammatory, antimicrobial, antiparasitic and antiviral effects [43].

We devoted publication 1 [1] to the botanical characteristics of the plant, to the problems of synonymy,

modern understanding of the chemical composition Sanguinaria canadensis L., on the use of thisplants in homeopathy, dentistry and veterinary medicine, as well as the experience of its nutritional use.

In this review, we have summarized the data on the traditional use of sanguinaria and presented the results of biological and medicopharmaceutical studies that allow us to evaluate the effectiveness of extracts from this plant in various diseases, including benign and malignant neoplastic processes.

The purpose of this informationanalytical research is the objectification of information about the spectrum of biological activity (in comparison with the experience of traditional use) and the prospects for the use of Canadian sanguinaria as a source of modern domestic drugs and / or phytonutrients.

MATERIALS AND METHODS

The objects of the research were normative documents recommended for use in the prescribed manner, and bibliographic sources of a high degree of reliability, including monographs, scientific periodicals, reference books, dissertations, dissertation abstracts, as well as electronic scientific and official databases. We also took into account Internet resources with links to bibliographic sources of a high degree of reliability.

When performing the work, the following research methods were used: information-analytical, historical, content analysis, systematization.

1. The use of Sanguinaria canadensis in traditional medicine

Sanguinaria canadian is a good example of a plant that has proven ethnobotanical and ethnopharmacological history of use in traditional medicine [43, 223]. According to experts, the history of traditional medical use provides valuable information for choosing models for further targeted research in order to develop new therapies and methods of treatment [61]. A very complete historical excursion to traditional medical applicationsS. canadensis is presented in [43], as well as on specialized professional Internet resources and in publications [24, 148, 178].

1.1. The use of sanguinaria by the indigenous people of the American continent

Historically, sanguinaria rhizomes were used by the American Indians to treat respiratory and gastrointestinal diseases and to terminate pregnancy in both humans and horses [24]. In general, Native Americans used sanguinaria to treat a wide variety of clinical conditions from the point of view of modern medical practice [43]. For example, the American Indians used rhizomesSanguinaria canadensis for the treatment of wounds and ulcers, croup, seizures, burns,tapeworms, fever, rheumatism, diarrhea, irregular menstruation, as well as in cough syrups, as an emetic (or antiemetic), and even as a "blood purifier" [24, 148, 149, 178].

Rhizomes have been reported to have been used in the form of teas and powders by a number of Indian tribes to treat colds, constipation, and flu-like symptoms. In large doses, it was used as an abortive and emetic tea; for the same purpose, a paste for oral administration was prepared from the rhizomes [24]. Some tribes had no idea about the dose-effect relationship, therefore, independently of each other, they used the rootsS. canadensis for opposite indications. For example, some tribesused minimal doses of sanguinaria root to stop vomiting [213], while other tribes used large doses as an emetic [206]. Large doses of the blood root were used by Indian women of different tribes as monotherapy for delayed menstruation [92], and also as an abortive agent [174].

There is evidence that several tribes used the blood root in the form of tea to treat colds and "chest congestion" (sometimes for this purpose the Indians inhaled powder from dried raw materials [92]) [43, 204]. Tribes that settled near the Rappahannok River used rhizome tea for detoxification in case of fever [43, 204].

Sanguinaria tea was also used to treat diphtheria [43, 203] and hemorrhagic tuberculosis [92]. At the same time, only a small piece of rhizome was added to the broth, since the Indians knew that large doses can cause poisoning [43]. Elderly Indians used tea from the underground organs of sanguinaria for rheumatism [43, 204].

A decoction of rhizomes mixed with a basil-shaped stalk, or blue buttercup (Caulophyllum thalictroides), American Indians used to treat spasms in the abdominal region [43, 49],

gastrointestinal bleeding and “lumps in the abdomen” [92].

Many tribes roots S. canadensis has been widely used as a topical therapy. For thisthey were boiled in water, the broth was cooled to body temperature and applied, for example, to wounds from an ax as a coagulant [92]. The decoction was also applied to wounds in the form of antibacterial poultices [43, 202].

From documentary evidence, the antibacterial properties of the blood root were well known to virtually all Native Americans, since they used its decoctions to treat any wound infections [34] and gangrene [142]. Many tribes used sanguinaria both internally and externally to treat ulcers, ringworm and skin infections [24].

The powder of the dried rhizome was also used by the Indians as an echarotik (cauterizing agent) when an antibacterial effect is required [43, 97]. The Mesquac Indians chewed the roots and then applied saliva to the burns to relieve pain [43, 202].

There is information about the traditional local use of the blood root by two tribes for the treatment of hemorrhoids: the Malehite Indians heated them in a small teapot, which was then used locally as a source of therapeutic steam [142], and the Cherokee Indians moistened tissue with a decoction for local applications [92].

In addition to medical purposes, American Indians, especially the Algonquian, Iroquois, and Siwan language groups, have historically used S. canadensis (called pukkon or pukkun [32, 43]) mixed with walnut oil or bear fat [43, 208] as a ritual face paint [148, 178, 208]. They also traditionally used sanguinaria to increase "love charm" [1, 74, 148,
149, 178, 208].

1.2. The use of sanguinaria by European settlers

European colonists, along with Native Americans, used S. canadensis extensively to treat a range of diseases and symptoms [61]. They were the first to describe the side effects of sanguinaria, indicating that the therapeutic or toxic effect of medicinal plants can directly depend on the dose [43]. For example, a dosage of about 1.29 g was used by migrants as an emetic [201], while as an antiemetic it was an order of magnitude less [43].

"Western" doctors began to use the bloody root out of necessity to treat diseases familiar to them among immigrants from Europe [116]. They also described the undoubted benefits of preparations from rhizomes, while attempts to use leaves and seeds were qualified by them as harmful, narcotic and toxic. These parts of the plant caused tremors, headaches, and numbness. The corresponding symptoms have been described by "Western" doctors as "intoxicating" or "narcotic" effect [43, 52].

In the treatment of respiratory diseases, rhizomes were used as a bronchial muscle relaxant in asthma [72], as an expectorant in the amount of 1–2 doses (one dose is equivalent to 64.5 mg of rhizome powder) every second hour [80], for the treatment of cereals [9, 43], whooping cough and even flu [58]. Oral use of sanguinaria rhizomes has been described as an antibacterial agent in the form of a decoction for the treatment of diphtheria and pneumonia [122], tuberculosis [43, 72], as well as in the form of an inhaled powder for the treatment of nasal polyps [123].

The blood root was also used by settlers to stimulate appetite [18], treat dysentery [214], functional dyspepsia [17], jaundice and chronic liver diseases [233], and even as a drug for alcoholism [128]. By analogy with the use of the Indians, "Western" doctors quite widely used sanguinaria to restore menstruation [59], to treat rheumatism, and also as an agent with anti-inflammatory properties [207].

A tincture of bloody root, rose water, and vinegar was prepared by the colonists and used externally as a treatment for eczema, ringworm, and facial acne. Extraction from raw materials with the addition of glycerin was used to rejuvenate hair follicles and prevent baldness [42]. Ointment based on nitric acid extraction fromSanguinaria has been used for pain relief and treatmentulcers of the skin, throat and anal fissures [42]. For the treatment of syphilitic chancre, the dried roots of sanguinaria were used in the form of a powder [19].

American surgeon Jesse Weldon Fell, who studied medicine with the Cherokee Indians living on the shores of Lake Superior, first discovered that zinc chloride enhances the action of sanguinaria rhizomes [65]. Experimentally, he found that the effectiveness of the plant extract can be increased by the addition of zinc chloride, if these components are mixed in equal parts with water to form a paste similar to molasses [63].

D.W. Fell first used the combination of these two agents to treat cancer on twenty-five patients at Middlesex Hospital in London in 1857. Most of the time it was cancer.

mammary gland [191]. Fell also pioneered the use of an ointment based on sanguinaria rhizomes in patients with lymph node metastases concurrently with oral extract therapyS. canadensis [65].

On the basis of independent clinical observations, surgeons at Middlesex Hospital concluded that zinc chloride was the only active ingredient in the bloody root paste, which, in their opinion, had no anti-cancer activity [147]. However, in 1857, Fell published the first report in the medical literature on the synergism of zinc chloride and sanguinaria in the journal Lancet [191]. In particular, he reported that of the 453 cancer patients he treated with the paste (many with advanced cases not suitable for surgery), the relapse rate was 27.5% after two years. The article argued that this was a significant progress (in 80% of cases) after two years, achieved by surgery, in relation to the frequency of relapses [65].

However, 25 patients independently observed at Middlesex Hospital showed a relapse rate over 9 months of only 21.4%. This called into question the accuracy of the Fells report over two years: if by the end of the 9th month the relapse rate was 21.4%, then the frequency of 27.5% by the end of two years was hardly possible [147]. Unfortunately, the relapse rate over two years for independently observed patients at Middlesex Hospital was not reported in publication [147].

Later, the study of the synergism of sanguinaria with zinc compounds was continued by Frederick E. Mosch [153] (section 2). According to [43], this synergistic combination, currently known as Black Salve, remains in topical use in the United States to this day.

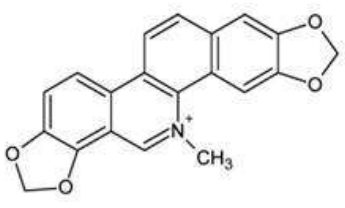
2. Modern concepts of the biological action of Sanguinaria canadensis L.

The most biologically active components of sanguinaria extracts are the alkaloids sanguinarine and chelerythrine. According to [115], it is they that exhibit antibacterial and anti-inflammatory properties [115], and also make the most significant contribution to the antitumor effect of rhizomes of sanguinaria canadensis [43, 69, 137, 136].

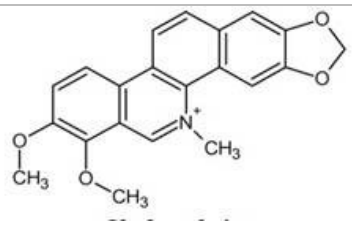
Sanguinarine ($C_{twenty}H_{fourteen}NO_4$ - rice. 1) is the most studied alkaloidS. canadensis. Describedits existence in two forms - in the charged form of iminium (pH 2–6) and in the uncharged form of alkanolamine (amino alcohol) (pH 6.5–9.0) [104, 133]. Both forms are in the range of physiological pH [15], but the second is more lipophilic and has a higher penetrating ability and bioavailability than the first [216]. The iminium form binds to nucleic acids, and high concentrations of nucleic acids cause an equilibrium shift that converts alkanolamine to the charged form of iminium [132]. Thus, sanguinarine is able to penetrate cells and accumulate in nuclei and nucleic acid-rich organelles, where it is activated to exert its intracellular action [197].

Chelerythrine is the second dominant alkaloid S. canadensis, which has two methoxylsubstituent at position C_{eleven} on the aromatic D-ring (Fig. 2).

Most of the available scientific publications discuss the anticancer effects of sanguinarine and chelerythrine [43, 69, 137, 138], as well as other alkaloids of S. canadensis [43]. Antimicrobial activity of sanguinaria is analyzed in works [43, 146], cardiovascular activity - in [129], neuroreceptor - in [43, 235], anti-inflammatory - in [175]. The review [188] also discusses other types of activity and the spectrum of biological action of individual BAS sanguinaria.



Rice. 1. Sanguinarine



Rice. 2. Chelerythrine

2.1. Antitumor activity of the alkaloids of sanguinaria canadensis

Sanguinarine. According to a study published by the University School of MedicineMinnesota, based on experience with Native Americans, it was found that the alkaloid sanguinarine from sanguinaria canadensis [1] can “block proliferation and induce apoptosis in a number of different transformed and malignant cell types” [50]. In particular, sanguinarine has been found to be effective in certain types of skin cancer, even when pharmaceutical

the drugs did not give a positive result [50].

The effect of sanguinarine was manifested through the effect on survivin, a protein that is specially produced to suppress cell death (apoptosis). When survivin is active in cancer cells, it can render them virtually invulnerable. Sanguinarine directly inhibited the function of survivin in cancer cells. This process included not only the creation of a balance within the cell, but also the direct cleavage of the survivin protein itself [50].

According to modern concepts, in leukemia, the spread of cancer cells in the blood is observed, and any substances that can cause apoptosis can be considered promising for the treatment of leukemia. In a study published in May 2016 in the journal Biology and Medicine of Free Radical Processes, it was shown that in leukemia, sanguinarine fromS. canadensis causes cancer cell deaththrough "activation of the caspase cascade, DNA fragmentation and suppression of anti-apoptotic proteins" in these cells [Cyt. by: 50].

A 2013 Korean study published in the journal Toxicology showed that the same processes (induction of mitochondrial dysfunction of cancer cells) are responsible for the effect of sanguinarine on tumor growth in colorectal cancer. A study at the University of California (2011) found that sanguinarine also has a pronounced effect on prostate cancer, mainly due to its effect on the protein survivin [Cit. by: 50].

In the already mentioned study at the University of Minnesota, it was also found that sanguinarine has an effect on breast cancer cells even after a single use. DNA synthesis in breast tumors (MCF7) resulted in inhibition of cancer cell growth. Some of the mechanisms of this inhibition were active for at least three days after a single administration (others only 24 hours). The results obtained allowed the researchers to conclude that sanguinarine can “suppress the proliferation of breast cancer cells for a long time” [50].

According to [43], sanguinarine interacts with DNA through intercalation (reversible inclusion of a molecule between other molecules or groups), having a binding coefficient comparable to anthracycline agents (antitumor anthraquinone antibiotics) daunorubicin and doxorubicin [14, 27, 145]. Its binding disrupts DNA polymerase, causing DNA strand breaks and cell death [3, 235]. It also prevents DNA strand break reconnection through depletion of nuclear topoisomerase II [93, 159], and this enzyme is a target for the chemotherapy drug etoposide [224].

Sanguinarine binds and closes telomeres, causing rapid apoptosis [13, 242]. It also binds G-quadruplex oncogenes (nucleic acid sequences enriched with guanine and capable of forming four-strand structures) cMyc, KRAS and Ckit, which leads to the termination of the cell cycle [44, 103, 230]. It was also revealed that this alkaloid targets the cell cytoskeleton, causing irreversible depolymerization of microtubules [127], which inhibits cell proliferation, which causes cell death [236].

According to [43], T-helical HDNA is present in hematologic malignant neoplasms cMyc and Bcl2 [114, 168] and is associated with worse outcomes in patients with colorectal cancer [155]. Sanguinarine binds to HDNA and damages it [47, 119]. It also inhibits the transition of B DNA to ZDNA, altering DNA supercoiling [119, 171]. In combination with its binding to the main histones, this leads to a change in the structure of chromatin and gene expression [73, 187].

Due to its direct genetic and epigenetic effects, sanguinarine alters gene expression in HeLa cells [187]. According to [187], exposure to a noncytotoxic concentration of 2 μM sanguinarine led to a decrease in the regulation of 378 genes, mainly involved in metabolic pathways. A total of 348 genes involved in cell signaling, cell adhesion, interaction with the extracellular matrix (ECM) receptor and complement coagulation were also activated by this concentration. Increasing the concentration to 5 μM activated a significant number of apoptosis genes such as DIABLO (direct inhibitor of apoptosis-binding protein with a low isoelectric point), while regulation of 225 genes was increased, while regulation of only 35 genes was decreased [187].

Sanguinarine also interacts with various RNA molecules. It strongly intercalates with messenger RNA (mRNA) poly (A), inducing the formation of its own structure, disrupting the transcription of poly (A) polymerase (PAP) [75]. Each sanguinarine molecule binds six base pairs of transfer RNA (tRNA) by intercalation, which further interferes with protein synthesis. Sanguinarine also tightly binds double-stranded RNA (dsRNA), which is involved in gene silencing and epigenetic regulation [38].

In addition to the above, in the experiment, sanguinarine influenced protein transcription, which was shown by proteomic analysis of pancreatic cancer cells BxPC3 when exposed to a concentration of 1 μM. Sanguinarine altered protein expression by more than 1.5-fold in about 5% of the 3107 identified proteins. A significant proportion of the proteins affected by this alkaloid were involved in cellular metabolism, with 61 proteins being activated and 87 proteins being suppressed [193]. This confirmed the pleotropic ability of sanguinarine to target a wide range of protein classes and target a variety of critical cellular processes. According to the results of experimental studies, the molecular pathway that is most susceptible to the influence of sanguinarine (or affected by sanguinarine) is protein ubiquitination [193].

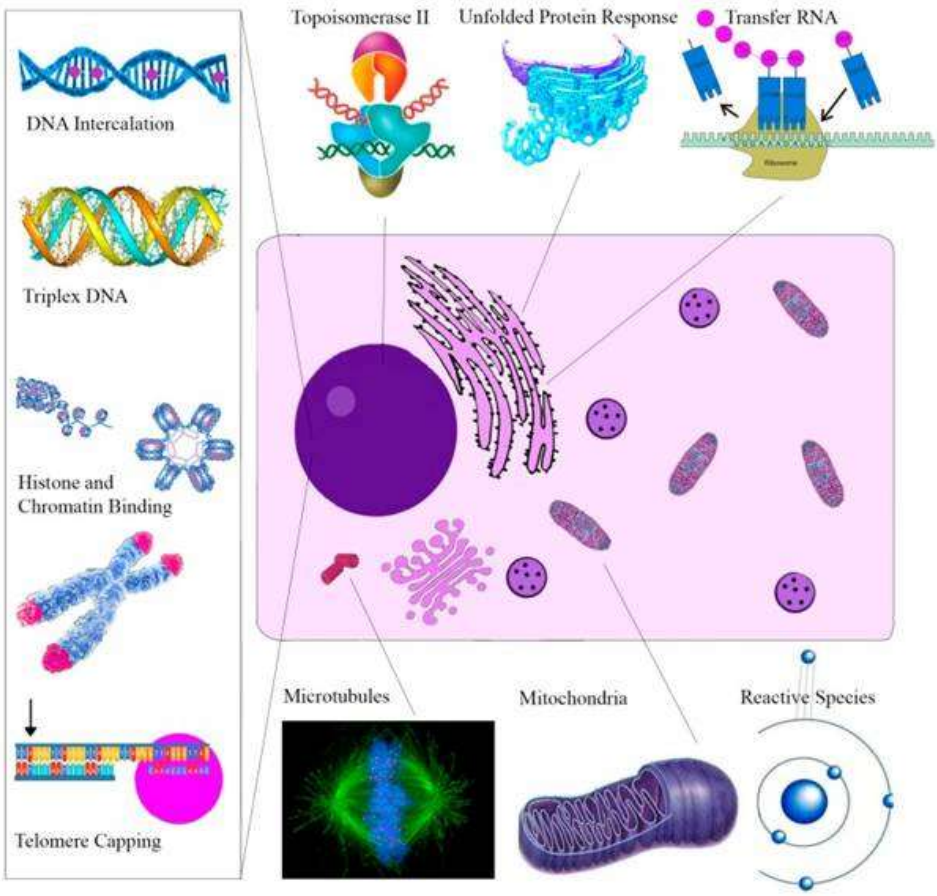
In 2008, it was shown that, in addition to direct action on cellular nucleic acids, sanguinarine has a cytotoxic effect on multiple cell lines through a significant generation of reactive oxygen species (ROS) [139]. Due to the redox cycle, apoptosis initiated by sanguinarine is independent of the p53 protein (a transcription factor that regulates the cell cycle; it acts as a suppressor of the formation of malignant tumors) [99]. However, conflicting results have been reported regarding the role of ROS in the cytotoxic effect of sanguinarine. Some researchers suggest that ROS play a critical role, while others have shown that sanguinarine inhibits oxidative surges through direct action on NADPH (nicotinamide adenine dinucleotide phosphate) oxidase.

When evaluating the antitumor effects of sanguinarine in the human lung adenocarcinoma cell line SPCA1, it was found that this alkaloid induces endoplasmic reticulum (ER) stress using ROS [81]. ROS cause unfolding or misfolding of proteins that accumulate in the ER lumen [134]. This triggers a molecular cascade called the unfolded protein response (UPR) [136]. Continuous ER stress promotes ROS production, creating a positive cytotoxic feedback loop [135]. Therefore, UPR has been identified as an anti-cancer target [177].

The works of E. Debiton et al. (2003) showed that sanguinarine also causes a rapid and significant decrease in glutathione (GSH) levels. Although glutathione is an antioxidant, the reported depletion was caused by the direct chemical exposure of sanguinarine to GSH, in which 50% of cellular GSH was degraded within 1 min after exposure to sanguinarine at a concentration of 5 μM [48]. Such significant GSH depletions may be apoptogenic by themselves [40, 82], and this reduction in cellular antioxidant reserves enhances damage from sanguinarine-induced ROS [43].

Another target to which the action of sanguinarine is directed is tumor growth due to neovascularization [109, 110]. At nanomolar concentrations, the alkaloid inhibits vascular endothelial growth factor A (VEGFA) -induced endothelial migration, germination, and survival of endothelial cells [51, 62].

Thus, sanguinarine targets a variety of cellular structures and molecular processes (Fig. 3), however, to date, the contribution of each mechanism to the cytotoxicity and anticancer effects of this alkaloid is not yet fully understood [43].



Rice. 3. Cellular targets of sanguinarine (according to [43]). The variety of cellular organelles and molecular processes disturbed by sanguinarine has been shown. Sanguinarine molecules (purple dots) the diagram represents the DNA intercalation image.

Chelerythrine. The chelerythrine molecule is less flat than sanguinarine and has a loweraffinity for DNA, compared to sanguinarine [14]. Nevertheless, chelerythrine is active against a number of human tumors [137, 138], including tumors resistant to radio- and chemotherapy [37], as well as p53-deficient tumors [33, 244].

Anti-cancer drug screening programs have identified chelerythrine as the leading candidate for cancer treatment. Of 107,243 extracts obtained from plants, actinomycetes, fungi, marine invertebrates and marine bacteria screened for their ability to degrade BclXL and BH3, 12 extracts had significant activity. Chelerythrine was a biologically active molecule with a specific effect in four studied plant extracts (with IC_{50} - 1.5 μM) [33]. A further study, which screened 6,700 mammalian target rapamycin inhibitors (mTORs), showed that chelerythrin has the greatest cytocidal effect on cells with mTOR overactivity [143].

Minor Quaternary Benzophenanthridine Alkaloids (QBA). Much less is knownon the biological activity of minor QBA [1], which are usually present in S. canadensis in morelow concentrations compared with sanguinarine and chelerythrine [43]. Sanguilyutin (Fig. 4) is more cytotoxic than basic QBAs with lower 50% inhibitory concentrations (IC_{50}) [83, 198].

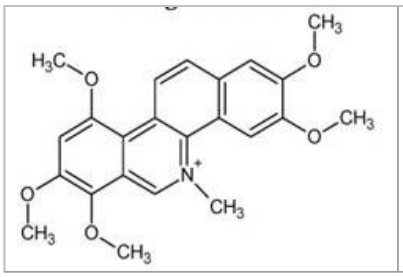
For IC_{50} in the range from 0.04 to 1.58 μg / ml, minor QBAs are active in therapeutically significant doses (Table 1).

Table 1

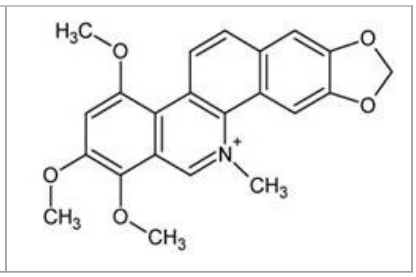
Comparison of cytotoxicity of dominant and minor
Quaternary benzophenanthridine alkaloids (QBA) S. canadensis (IC_{50}) (according to [43, 198, 200])

Alkaloids (IC_{50}, μg / ml)	HL-60	HeLa	KF-II	A431
Sanguilyutin	0.04	0.46	-	-
Sanguirubin	0.12	0.68	0.22	0.7
Helilyutin	0.16	0.84	-	-
Helirubin	0.10	0.37	0.20	0.28
Sanguinarine	0.34	0.70	0.50	0.70
Chelerythrine	0.17	0.48	0.58	1.44

According to [43], minor QBAs act through molecular processes that differ from the mechanisms of action of the main (dominant) QBAs. Helilyutin (Fig. 5) acts as a strong inducer of apoptosis without generating ROS [83], while sanguilyutin (Fig. 4) causes death of melanoma cells through necroptosis [84]. Necroptosis is a new non-apoptotic caspase-independent programmed cell death facilitated by receptor-interacting protein kinase 1 (RIP1) [220]. Sanguilyutin activates RIP1, which leads to the formation of Ripoptosomes (RIP1, FADD, and caspase8) and, subsequently, to cell death [84]. Cancer cells are often resistant to therapy due to altered apoptotic mechanisms. According to [43], interest in compounds such as sanguilyutin, which act in alternative pathways, is constantly growing.

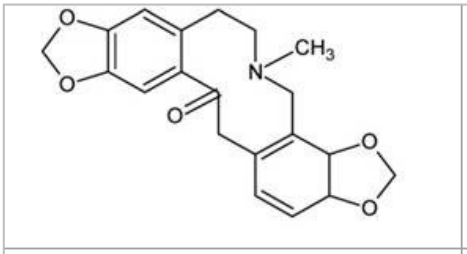


Rice. 4. Sanguilyutin

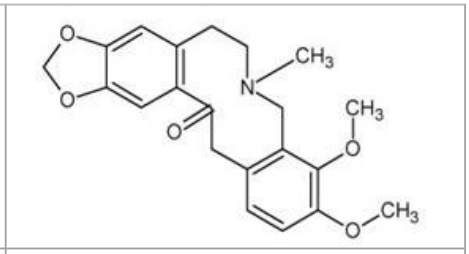


Rice. 5. Helilyutin

Protopine alkaloids. Unlike benzophenanthridines [1], protopine alkaloids (Fig. 6) have a minimal antiproliferative effect on a number of cancer cell lines (Sun et al., 2014, cited from [43]). Protopin (Fig.6a) relieves oxidative stress and apoptosis, in part due to antioxidant mechanisms and Ca antagonism^{2+}[238], therefore, it can counteract the cytotoxic action of other alkaloids of sanguinaria. In [91], it was shown that protopin attenuates the invasion of cancer cells and the metastatic potential of MDAMB 231 breast cancer cells by reducing the expression of adhesion molecules such as the epidermal growth factor receptor (EGFR), ICAM1, and integrins.



a) Protopin



b) Allokryptopin

Rice. 6. Protopine alkaloids

table 2

The anticancer effect of alkaloids S. Canadensis (by [43])

Molecular target	Cellular effect / role in the mechanism antitumor action	Bibliographic a source
Sanguinarine		
Topoisomerase II	Prevents DNA repair	[93]

Molecular target	Cellular effect / role in the mechanism antitumor action	Bibliographic a source
Telomere coverage	Causes rapid apoptosis	[243]
Oncogenes Cmyc, KRAS, Ckit	Expressed in various tumors	[103]
NDNA	Hematologic and Colorectal Tumor Expression	[47]
Bcl2 family	Induction of apoptosis	[5]
ERKs	Induction of apoptosis	[86]
NFkB	Role in proliferation, migration, apoptosis	[35]
DR5	TRAIL-mediated apoptosis	[98]
Endoplasmic reticulum	Expanded protein response	[81]
VEGFA	Worsens tumor neoplasm	[62]
Glutathione	Exhaustion increases oxidative stress	[48]
Antimicrotubules	Inhibits cell proliferation	[127]
Chelerythrine		
BclXL and Bcl2	Induction of apoptosis	[33]
Telomere coverage	Causes rapid apoptosis	[71]
Succinate	Cytochrome with release	[16]
NADH dehydrogenase	Assembly of apoptosomes	[16]
Glutaminase	Blocks the tumor. Glutamine is used for energy production	[215]
mTOR	Overexpression in melanoma	[143]
Phospholipase D	Associated with angiogenesis / metastasis	[192]
MRCK	Decreases tumor migration	[210]
Tubulin polymerization	Decreases cell division	[236]
MARK	Activation leads to apoptosis	[246]
Minor QBA		
RIP1	Ripoptosome formation	[84]
Unknown	Apoptosis ROS independent	[83]
Antimicrotubules	Disruption of mitosis	[199]
Protopine alkaloids		
Antioxidant effect	May counteract the cytotoxic effects of other alkaloids	[237]
EGFR / ICAM1	Decreased expression worsens metastasis	[91]

Despite a similar chemical structure, alkaloids present in S. canadensis [1], have a significant number of unique molecular features (Table 2). Sanguinarine (Fig. 1), for example, is a potent inhibitor of NFκB, while chelerythrine (Fig. 2) has no NFκB activity [35]. Back in 2008, PH Bernardo et al. found that when alkaloids have a common molecular target, they can bind to different parts of the molecule, for example, as is the case with the protein that promotes the survival of BclXL [22]. However, the effect of simultaneous action on the target with various alkaloids has not been studied in detail. The question of whether alkaloids will exhibit antagonistic action or, on the contrary, reinforce each other when destroying targets remains unresolved, although, according to experts, it has a direct clinical significance [43].

2.2. Anti-inflammatory effect of sanguinaria alkaloids

In works [43, 160], it was shown that chelerythrine has an anti-inflammatory effect, inhibiting the production of COX2 and PGE2 [160]. The COX2 inhibitory activity of chelerythrin was comparable to NS398, a specific COX2 inhibitor. Chelerythrine also had an effect on the inhibition of 5-lipoxygenase [221] and the weakening of oxidative release [194, 225].

According to [43, 232], polymorphonuclear leukocytes (PMNs) release cytokines and lytic enzymes that induce inflammation; however, when PMNs undergo apoptosis, they are removed by the reticuloendothelial system without releasing an inflammatory mediator [232]. In [79, 90, 181], it was shown that PMN apoptosis is the main mechanism for resolving inflammation in the intestine, lungs, joints, and kidneys [43, 90, 181]. Chelerythrin induces rapid apoptosis in human PMN through an independent PKC (protein kinase C) mechanism, preceded by rapid activation of caspase 3. A dose of 10 μM chelerythrine chloride induces rapid and significant PMN apoptosis in less than 4 hours [209].

Intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) facilitate neutrophil migration into tissues [8] and are key components of inflammatory diseases such as asthma [154] and inflammatory arthritis [212, 219, 241]. Testing of 40 natural and synthetic alkaloids, terpenoids and phenols has shown that Sanguinarine and Isoliquiritigenin significantly reduce VCAM1 levels. Of the 10 compounds studied that suppressed ICAM1, sanguinarine had the greatest effect, decreasing expression by 50.6% [211].

In an experiment with protopine alkaloids [12, 43] inflammation induced pro-inflammatory enzymes such as COX2, NO and PGE2, as well as the inflammatory cytokines TNFα, interleukins IL1 and IL6. Protopin had an anti-inflammatory effect, being a potent NO inhibitor, downregulating COX2 expression and impairing the production of PGE2, IL1B, IL6 and TNFα. This occurred through inhibition of ERK 1/2 and JNK phosphorylation and activation of NFκB in murine macrophages [12]. It was also found that protopin inhibits carrageenan-induced rat paw edema with an activity three times higher than that of acetylsalicylic acid [175].

2.3. Antimicrobial action of S. canadensis alkaloids

The review [43] summarizes data on the pronounced antimicrobial effect of both benzophenanthridine [1] and protopine alkaloids S. canadensis. In particular, in [161] showed that sanguinarine induces the release of autolytic enzymes associated with the membrane wall of the bacterial membrane, which leads to activity against methicillin-resistant Staphylococcus aureus (MRSA) with a minimum inhibitory concentration (MIC) for two control strains: 1.56 μg / ml and 3 , 12 μg / ml [161]. Sanguinarine also has bactericidal activity against gram-negative and gram-positive organisms that are resistant to vancomycin. Moreover, coadministration of sanguinarine with vancomycin made organisms susceptible to vancomycin [85]. When testing 64 different types of microorganisms in the oral cavity, the MIC of sanguinarine varied from 1 to 16 μg / ml for 98% of isolates [55].

Considering that Helicobacter pylori plays a pathogenic role in gastritis and peptic ulcer disease with increased level of resistance to modern combined antibiotic therapy [77], the results of two studies are of particular relevance [77, 131]. In particular, in [131], the total methanol extract of rhizomesS. canadensis demonstrated MIC 50 against H. pylori, in concentration
12.5 μg / ml. At the same time, individual alkaloids were less effective - with MIC 50 values at concentrations of 50 μg / ml for sanguinarine and 100 μg / ml for chelerythrine and protopine. Researchers suggest that alkaloids may exhibit synergistic effects [43, 131].

When studying the antimycobacterial activity of 43 plant species traditionally used for the treatment of tuberculosis, a pronounced antimycobacterial effect of the extracts was revealed. S. canadensis.When analyzing the activity of individual components, it was found that chelerythrine is the most active with IC_{50} 7.3 μg / ml (19.02 μM) versus Mycobacterium aurum. Sanguinarine is second on the listmost active substances with IC_{50} 9.61 μg / ml [43, 158].

2.4. Antiparasitic activity of sanguinaria alkaloids

Schistosomiasis is a snail-borne parasitic disease that affects over 200 million people worldwide. In the United States and some other countries, this helminthiasis is usually treated with Praziquantel [190], which is practically ineffective in the early stages of the disease [43], and schistosome resistance is noted in a number of endemic areas, such as Egypt [100]. When testing 45 compounds, sanguinarine was one of two compounds where a concentration of 10 μM led to 100% death of parasites after 48 hours, which met the criteria for "hitting" the compound in the number of effective substances according to the World Health Organization (WHO)

[245].

A pronounced antiparasitic effect (exceeding the effectiveness of synthetic drugs) of protopine alkaloids (Fig. 6) of sanguinaria in relation toStrongyloides stercoralis - a parasitic infection that infects 100 million people in tropical areas around the world [180, 182, 186].

The urgency of the problem and parasitic invasions in aquaculture for fish is constantly growing. The most at risk of infection are freshwater fish, which are usually infected with gill monogens, especially Dactylogyrus [106]. It was found that sanguinarine has the highest activity in relation to alkaloids of macleia large-fruitedMacleaya microcarpa (Maxim) Fedde withThe EU_{50} 0.37 mg / l. Less potent effects have been reported for 6methoxyldihydrochelerithrin 3.63 mg / L, allokryptopin 4.64 mg / L, and protopin 8.13 mg / L [227].

Anthelmintic Effects of Alkaloids on Roundworm Toxocara canis have been researched inveterinary medicine in dogs [43]. To date, only a few anthelmintic agents are effective against nematodes, and they are often only active when they are directly present in the gastrointestinal tract [43].

Pyrantel (Pyrantel pamoate) has a relative mobility of 50% (RM_{50}) inhibition of intestinal Toxocara canis in concentration 46 μmol / l. A pronounced anti-nematicidal activity was observed in the experiment for 6methoxyhydrosanguinarin - RM_{50} 18 μmol / l, chelerythrine - RM_{50} 28 μmol / L and sanguinarine - 58 μmol / L [179]. However, the authors of the study [179] argue that due to cytotoxicity against HL60, these agents (with IC_{50} for 6methoxyhydrosanguinarin - 0.3 μmol / L, chelerythrine - 0.2 μmol / L and sanguinarine - 0.5 μmol / L) are less suitable for the role of medicinal substances in comparison with other compounds, even if less effective, but do not exhibit cytotoxicity ...

However, according to I. Slaninova et al. (2014), the HL60 cell line, chosen in this case to determine the cellular toxicity of alkaloids, is more susceptible to alkaloid damage than non-malignant cells, and, possibly, this leads to an overestimation of the potential risk of toxicity of sanguinaria alkaloids [196].

Allokryptopin (Fig.6b) had RM_{50} 349 μmol / L and IC_{50} 48 μmol / L. The lowest RM coefficient set for it $_{50}$/ IC_{50} allowed the authors of the study [179] to recommend this compound as the most promising natural agent for further pharmaceutical development [179].

2.5. Antiviral, antiplasmodial and antifungal activity of sanguinaria alkaloidsA screening study of 2000 drugs and natural substances described in [36] showed that sanguinarine has antiviral activity that inhibits HIV protease with IC_{50} 13 μM [36]. Sanguinarine is also active against the herpes simplex virus, while both protopine alkaloids, protopine and alcryptopine, are active against parainfluenza virus3 [163].

In the experiment, protopin shows very promising antiplasmodial activity against wild-type P.4 strains and strains Multidrug-resistant P. falciparum (K1) with IC_{50} 1.5 μg / ml [228]. It has been shown that chelerythrine and sanguinarine are especially active against trypanosomeT. brucei - causes of sleeping sickness with EC_{50} 1.3 and 4.8 μM, respectively [173].

The antifungal activity of protopin is still not entirely clear: one study showed minimal activity [144], while another showed strong inhibition Candida albicans when exposed 4 μg / ml [163].

2.6. The effect of sanguinaria alkaloids on the cardiovascular system

A review of the effect of sanguinaria alkaloids on the activity of the heart and blood vessels is presented in [43]. It has been shown that sanguinarine has a vasodilating effect, inhibiting α1 and α2 adrenergic receptors with IC_{50} 33.6 and 6.4 μM, respectively [184]. In particular, in a study of 19 Panamanian plants used as traditional medicines for the treatment of hypertension, the extractBocconia frutescens L. containing sanguinarine [28] inhibited the binding of angiotensin II by 50% [29]. It was also revealed that sanguinarine blocks angiotensin II in a slow, almost irreversible and non-competitive manner [30]. Protopin also has a vasodilator effect, increasing the level of cAMP and cGMP [125].

In work [185] it was shown that several alkaloids of sanguinaria canadensis interact with the ion channels of the heart. Sanguinarine with IC_{50} 6.0-6.5 μM inhibits Na activity^{+}K^{+}ATPases, like digitalis cardiac glycosides, in particular digoxin. In the atria of guinea pigs, this increases

intracellular Na^+, activating the exchange Na^+/ Ca^{2+}leading to an increase in intracellular Ca levels^{2+}... A dose of 10 μM has a positive inotropic effect [185].

Protopin acts as an inhibitor of heterogeneous cation channels in guinea pigs by blocking Ca channels^{2+}, K^+ and Na^+ [205], while allocryptopin blocks K^+ channels in rabbit ventricular myocytes [124]. It was found that allokryptopin is even more effective than quinidine in the prevention of induced arrhythmias in rats [7].

Chelerythrin in cultured neonatal rat heart myocytes induces apoptotic death at a concentration of 6–30 μM due to the formation of ROS [240].

2.7. Other types of action of alkaloids of sanguinaria canadensis

Studies [6, 169, 226] have demonstrated the antioxidant and protective effect of sanguinarine against damage caused by ultraviolet (UV) B radiation. This suggests that it may play a role in the prevention of skin cancer [6].

A protective effect against UVB damage has been shown in female SKH1 hairless mice. Topical application of 5 μmol sanguinarine as pretreatment (30 minutes before UV exposure) or after treatment (5 minutes after UV exposure) significantly reduced ultraviolet-induced skin edema, hyperplasia and leukocyte infiltration [6]. Sanguinarine was shown to induce apoptosis in UVB-damaged HaCaT keratinocytes [169]. It was revealed that sanguinarine also has an antioxidant effect, realized through inhibition of oxidative bursts in inflammatory cells. In this case, the alkaloid acted not as a scavenger of free radicals, but through the pathway of destruction of NADPH oxidase [226].

The review [43] presents data on the presence in alkaloids S. canadensis, neurotransmitter,local anesthetic, gastrointestinal, coagulating types of action.

In particular, research in vitro and in vivo made it possible to qualify protopin (Fig. 6a) and allocryptopin (Fig. 6b) as potent inhibitors of acetylcholinesterase [111, 112]. While galantamine has a 49% inhibitory effect on acetylcholinesterase, allocryptopin and protopin cause significantly greater inhibition - by 89.31% and 80.53%, respectively [189].

Chelerythrine has been investigated as an effective agent for reducing insulin resistance. In an experiment in mice, it more strongly blocked the phosphorylation of the peroxisome proliferator-activated gamma receptor (PPARγ) compared to thiazolidinedione (TZD) preparations. It is assumed that the transcriptional profile of chelerythrin reduces side effects when compared to the TZD drugs used today [247].

Protopin has shown good potential as a neuroprotective agent in stroke and as an antidepressant. It was found that protopin reduces the level of glutamate in the brain by 23% due to an increase in glutamate dehydrogenase (GDH) by 1.6 times [121]. Excitotoxicity (a pathological process leading to damage and death of nerve cells under the influence of neurotransmitters) glutamate and calcium overload have been implicated in the pathophysiology of stroke. According to the authors of the study, protopin increases serum superoxide dismutase activity, which indicates its neuroprotective effect, partially related to the antioxidant properties of this alkaloid. Protopin has also been suggested for the treatment of mood disorders as it appears to inhibit the serotonin transporter (SERT) and the norepinephrine transporter (NERT) [239].$_{50}$11.8 and 91.7 μM, respectively [184].

One percent solution of alkaloids isolated from Macleaya cordata (Wild.), The main component of which is allokryptopin (Fig. 6b), has a local anesthetic effect [60], stronger than procaine at a similar concentration [76]. Allocryptopin appears to induce a relaxing effect on the guinea pig ileum by inhibiting phosphodiesterase, but has a contractile effect through its interaction with the α adrenergic receptors on the urinary bladder [2].

Protopine is a weak anticholinergic alkaloid, which is 660 times less effective than atropine, but still has antispasmodic (antispasmodic) and relaxant effects on smooth muscles [218]. Sanguinarine blocks muscarinic receptors with IC_{50} 2.4 μM [184].

Protopin also appears to act on platelets having a lower IC_{50} against various platelet agonists such as arachidonic acid and platelet activating factor than those observed for aspirin [175]. While protopin selectively inhibits the synthesis of thromboxane A2, sanguinarine inhibits the production of thromboxane B2 [102].

3. Application of Sanguinaria canadensis L.

in modern world medical and pharmaceutical practice

According to the PDR for Herbal Medicines (2007), the alkaloid sanguinarine has antimicrobial and anti-inflammatory effects [166]. The efficacy of sanguinarine from sanguinaria rhizomes when used as an agent against plaque and gingivitis is considered to be reliably proven [166]. Sanguinarine products were widely used in the United States as a component of toothpastes and mouth rinses [24, 50, 87, 166], but [43], with reference to [222], it was reported that these drugs caused leukoplakia and were therefore withdrawn from the market. ... A detailed review of the medical use of products from Canadian sanguinaria in dentistry is presented in [1].

Alkaloids S. canadensis are allochemicals (altering the originalchemical composition due to the introduction or removal of a substance) of a phytoalexin nature (synthesized by plants in response to the penetration of pathogenic microorganisms), capable of disrupting multifaceted cellular processes [43]. Today, there are difficulties with the use of blood root alkaloids as official (pharmacopoeial) drugs due to the problems associated with their potential toxicity. However, their ethnopharmacological history suggests the possibility of developing drugs with therapeutically effective doses and with adequate levels of toxicity acceptable to patients [43].

According to the data of the already mentioned American medical manual [166], monocomponent preparations from sanguinaria canadensis were previously used as expectorants [166], and now the rhizomes of sanguinaria are part of a number of multicomponent preparations for cough [178, 54].

Sanguinaria extract was also used topically in the composition of "black ointment" in monotherapy for skin cancer [43]. However, according to some reports, the use of the ointment was accompanied by therapeutic failures [120] and was limited by its toxicity [57].

According to other sources, the use of this ointment can still be considered relevant [43]. In particular, Internet sellers are still selling "black ointment" based onS. canadensis for local therapycancer [43, 101]. However, today there are serious doubts about the effectiveness of the "black ointment" due to the lack of its standardization. In particular, as a result of the use of this ointment [140], there have been reports of cases of extensive tissue destruction and recurrence of the disease, leading to death [162]. Of the two histologically confirmed cases of melanoma treated with black ointment, both patients developed metastatic disease [39].

Perhaps this is due to the falsification of the ointment and the fact that unscrupulous sellers do not report the composition of the "black ointment", using only its popular name. In particular, to date, only one study of the chemical composition of a single sample is known, and this was only an assessment of the qualitative composition without determining the concentration of ingredients [164].

According to [43], in practice, the composition of the ointment varies. For example, in the laboratory of Alpha Omega Laboratories 2 methods of treatment are used - "Kansema" (Cansema) and / or "Amazon" (Amazon). The ointments used in this case contain zinc chloride, as well as extracts of sanguinaria rhizomes (S. canadensis), chaparral leaves (Larrea mexicata), graviola (Annona muricata), oleander (Nerium oleander) andglycerin [31]. And the oral anticancer tonic from Cansema (Amazon) Tonic III does not include sanguinaria rhizomes at all as an ingredient [43].

Despite vendors claiming more than 98% cure rates for skin cancer, there are currently no reported clinical data on successful trials of “black ointment” with minimal adverse reactions [31]. However, some suppliers are confident in suggesting the use of black ointment for the treatment of melanoma [31, 56].

If we recall the clinical trials of "black ointment" at Middlesex Hospital in London (section 1), it should be noted that the release to the public of unverified test results of anti-cancer drugs based on the blood root was not an isolated event in the history of the study of this plant [43].

At the beginning of the 20th century, Harry Hoxsey [105] also promoted drugs containing S. canadensis as a cancer therapy. Hoxsey used two methods of local(external) therapy: 1) yellow powder containing arsenic sulfide, sulfur, talc, yellow precipitate; 2) red paste containing bloody root, antimony trisulfide and zinc chloride [96]. In addition, for the treatment of malignant neoplasms of internal organs, tonics were used that did not containS. Canadensis [105]. Hoxsey did not conduct any clinical trials, only one observational study, conducted in 1983, followed 39 cancer patients for 5 years. However, by the fifth year from the beginning of the study, 58.9% of patients were lost to follow-up [11].

A progressive cohort pilot study of 149 patients receiving Hoxsey cancer treatment at the Tijuana Biomedical Clinic was conducted in 1992. According to the results of the analysis from the standpoint of evidence-based medicine, only 43.6% of the records contained messages, covering only 57% of patients, about patients with pathology with a 5-year life status. After 5 years from the start of the study, only 11.4% of patients were alive, while 45.6% died. The study results for 42.9% of patients remained unknown [172]. Such clinical studies, according to experts, highlight the lack of appropriate "scientific rigor" of clinicians offering drugs for the treatment of cancer. The unknown status of a significant number of patients is also alarming, which does not allow an objective assessment of the effectiveness of treatment [43].

According to the review [43], today all monopreparations from the rhizomes of sanguinaria canadensis in most countries are considered obsolete and / or having controversial toxicity. Sanguinaria extracts are currently used only in multicomponent pharmaceutical preparations (as one of the ingredients), or in veterinary medicine [1, 43, 115, 166].

According to other data, the rhizomes of sanguinaria continue to be actively studied and are used as agents for the treatment of skin cancer and warts [24]. In particular, in the already mentioned study [50], published by the University of Minnesota School of Medicine, it was shown that the prescribed dosage of sanguinarine is effective in certain types of skin cancer, even when officially used pharmaceuticals are not effective. According to [50], "sanguinarine is of particular interest from a chemotherapeutic point of view, since it inhibits the growth of squamous cell carcinoma cells more effectively than the growth of normal keratinocytes (the main cell type of the epidermis) and inhibits the growth of a number of multidrug-resistant cell lines."

As early as 1932, Frederick E. Mohs (Mohs), investigating the reaction of cancerous and normal tissues to various stimuli, noticed that a 20% solution of zinc chloride ($ZnCl_2$) chemically "killed" tissues, while maintaining their histological structure [153]. Mohs believed that the recurrence of skin cancer occurred as a result of the presence of tumor cells on the surgical margin, which were not detected by standard histological procedures, which controlled only 1% of the excised lesion [113]. Therefore, he developed a fixing paste based on $ZnCl_2$, which would histologically preserve human tissue and control the tumor process. He also found that the extract from rhizomesS. Canadensis and stibnite (stibnite) stabilized the paste [217], allowing it to function as a reservoir that slowly releases zinc chloride into the surrounding tissue [150].

The indicator of 5-year clinical application of Mohs's paste using the fixed tissue method for basal cell carcinoma (BCC) in 7257 cases was 99.3%, and for squamous cell carcinoma (SCC) in 2551 cases - 94.4%. This impressive result was achieved even in those 20% of patients who had recurrent tumors after previous surgery or radiation therapy [152].

However, objectification of these data showed that the high rates achieved using the Mohs technique are associated only with complete histological control of the excision margins, and not with the anticancer effect. S. canadensis. The conclusion was confirmed by subsequent research,which showed equivalent efficacy, in which the operation with the controlled edge was performed without fixing paste [151].

Unfortunately, the rational design of clinical trials of drugs today, as a rule, focuses on one compound and one target in order to minimize the unwanted side effects that may arise from binding to secondary targets [95]. However, these selective approaches to evidence-based medicine have to be and have been questioned by the effectiveness of the application of the experience of traditional medicine in clinical practice [43, 94]. According to the most modern concepts, herbal extracts (extracts, tinctures, powders from medicinal plant materials, etc.) can not only reduce the risk of toxicity of certain biologically active substances, but can also treat the disease itself, and no less effectively than individually isolated compounds [43].

Controversial cytotoxicity is of concern due to the use of a variety of products under the guise of “black ointments”. One studyin vitro showed that sanguinarine hasconcentration-dependent therapeutic window. At a concentration of 2 μM, sanguinarine exhibits preferential cytotoxicity against the A431 squamous cell carcinoma cell line compared to normal keratinocytes. However, this selective cytotoxicity to tumor cells is lost already at a concentration of 5 μM [4].

Other studies have not confirmed the results of this experiment. In particular, in [48]

described the experimentally established equivalent cytotoxicity of sanguinarine between tumor and normal cell lines. And in the study [198], this alkaloid actually had an even greater cytotoxic effect on skin fibroblasts than on the same A431 cell line that was used in [4].

According to clinicians, even if there is a therapeutic window for sanguinarine, it is doubtful that natural alkaloids, in total, isolated directly from rhizomes S. canadensis(taking into account their variable alkaloid composition [1]), can be strictly targeted at a pharmacologically narrow target. Therefore, in any case, standardization is always required (analysis of the qualitative and quantitative composition of the ointment) in order to reliably assess the effect of alkaloids on each patient. It is the lack of standardization that seems to explain the persistence of skin cancer due to subtherapeutic levels of alkaloids and extensive tissue necrosis due to toxic concentrations of alkaloids [43].

Generalized ideas about the possibility of using sanguinaria in modern medico-pharmaceutical practice were presented by D. Duke JA in the second edition of the Handbook of Medicinal Plants [54] (Tables 3, 4).

Table 3

Biological activity and types of pharmacotherapeutic action of canadian sanguinaria (in alphabetical order) (after [54])

No. p / p	Type of action, clinical effect	Evidence-based base (according to [54])	Note
1	Abortive	f (in large doses)	No scientific evidence, only data from traditional / traditional medicine
		CEB	[170]
		DEM	[149]
2	Aphrodisiac (aphrodisiac)	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
3	Analgesic	f	No scientific evidence, only data from traditional / traditional medicine
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
		DEM	[149]
4	Anesthetic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		CRC	[53]
5	Antibacterial	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
6	Antiseptic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]

		CAN	[156]
		PH2	Effectiveness confirmed by Commission E (KOM) [80]
		PHR	Effectiveness confirmed by Commission E (KOM) [68]
7	Anticholinesterase	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		HH3	[89]
eight	Inducing sneezing	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
nine	Antipyretic	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
ten	Choleretic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		FEL	[66, 67]
eleven	Coloring	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
12	Eliminating stagnation	f	No scientific evidence, only data from traditional / traditional medicine
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
13	Diuretic	f	No scientific evidence, only data from traditional / traditional medicine
		CEB	[170]
		CRC	[53]
fourteen	Narcotic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		CRC	[53]
		PHR	Effectiveness confirmed by Commission E (KOM) [68]
15	Cleaning	f	No scientific evidence, only data from traditional / traditional medicine
		DEM	[149]
16	Expectorant	f	No scientific evidence, only data from traditional / traditional medicine
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
		CAN	[156]
		HH3	[89]
		PHR	Effectiveness confirmed by Commission E (KOM) [68]

17	Paralytic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		PHR	Effectiveness confirmed by Commission E (KOM) [68]
eighteen	Diaphoretic	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
		CEB	[170]
19	Raising heart activity	f	No scientific evidence, only data from traditional / traditional medicine
		DEM	[149]
		CAN	[156]
		HH3	[89]
twenty	Positive inotropic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		HH3	[89]
21	Hindering dental education plaque	PDR	Data from the PDR for Herbal Medicines (Ed. 45, 1991) [165]
		PHR	Effectiveness confirmed by Commission E (KOM) [68]
		PH2	Effectiveness confirmed by Commission E (KOM) [80]
		1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
22	Anti-inflammatory	1	Also
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
		HH3	[89]
23	Antineoplastic	APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
		COX	[157]
		Fnf	Duke JA Phytochemical Database, (USDA: www.arsgrin.gov/duke) (USDA: www.ars grin.gov/duke) [64]
		1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
24	Decongestant	HH3	[89]
		1	Evaluation of effectiveness: a chemical in the plant or plant extract has been shown to be active - or has been proven to be active

		1	experimentally (on animals), or in vitro; butno evidence of clinical efficacy yet
25	Antiparasitic, in including anthelmintic	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
		DEM	[149]
26	Antiemetic		At the same time, emetic, depending on the dose [54]
		f	No scientific evidence, only data from traditional / traditional medicine
		DEM	[149]
27	Emetic		At the same time antiemetic [54]
		APA	Data from American Pharmaceutical Association - American Pharmaceutical Association [167]
		CAN	[156]
		PH2	Effectiveness confirmed by Commission E (KOM) [80]
		PHR	Effectiveness confirmed by Commission E (KOM) [68]
		1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
28	Sedative	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
29	Artery sedation	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
thirty	Secretolytic	FEL	[66, 67]
		1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
31	Laxative	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
		CAN	[156]
32	Antispasmodic		At the same time, spasmodic [54]
		CAN	[156]
		f	No scientific evidence, only data from traditional / traditional medicine
33	Spasmodic	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		PHR	Effectiveness confirmed by Commission E (KOM) [68]

			At the same time, antispasmodic [54]
34	Stimulating	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
35	Stimulating menstruation	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
36	Tonic	f	No scientific evidence, only data from traditional / traditional medicine
		DEM	[149]
		CRC	[53]
37	Firming	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
38	Cutting rhythm heart rate	f	No scientific evidence, only data from traditional / traditional medicine
		CRC	[53]
39	COX2 inhibitory	1	Evaluation of effectiveness: a chemical in a plant or in an extract of a plant has been shown to be active - either it has been proven experimentally (in animals), or in vitro; butno evidence of clinical efficacy yet
		Fnf	Duke JA Phytochemical Database, (USDA: www.arsgrin.gov/duke) (USDA: www.ars grin.gov/duke) [64]
		COX	[157]

Note to table 3-5:
AHP - data from American Herbal Products Association - American Herbal Products Association (AHP) [141].
APA - data from American Pharmaceutical Association - American Pharmaceutical Association [167].
CAN - publication data [156].
CEB publication data [170]. COX - publication data [157]. CRC - edition data [53]. DEM - publication data [149]. DEP - data of the edition [229]. FEL - publication data [66, 67].
FNF - Duke JA phytochemical database (USDA: www.arsgrin.gov/duke) [64]. HDR - data from Herbal Desk Reference Duke JA - "Desktop reference book of medicinal plants" for the program of medical botany by J. Duke - author's online version.
HHB - edition data [126].
HH3 - publication data [23].
JLH - edition data [89]. MAD - publication data [138].
PDR - Data from the PDR for Herbal Medicines Ed. 45, 1991 [165].
PHRs are Commission E (KOM) approved plants included in the 1st edition of the PDR for Herbal Medicines [68].
PH2 are Commission E (KOM) approved plants included in the 2nd edition of the PDR for Herbal Medicines [80].
PIP - can be used in pediatrics (based on Hans Schilcher's monograph "Phytotherapy in Paediatrics") [183].
PNC - edition data [234].
USDA is the USDA nomenclature database (www.arsgrin.gov).
WAM (MOM) - can be used in pediatrics (based on the monographs of Dr. Linda White (MD) and Sunny Mavor "Kids, Herbs, Health") [231].

1 - Evaluation of effectiveness: the chemical in the plant or in the extract of the plant has shown activity: either its presence has been proven experimentally (in animals), or in vitro; however, there is still no evidence of clinical efficacy [54].
2 - Evaluation of effectiveness: an aqueous extract, decoction or tea from the plant, possibly also - ethanol extraction showed activity, which was also supported by proven effectiveness in clinical trials. In most cases, the effectiveness has been proven and approved by the Commission E (KOM) and Tramil Commission (TRA) [54].
f - Evaluation of effectiveness: activity data available from traditional or traditional medicine; however, adequate scientific research has not yet been carried out [54].

From the data table. 3 it can be seen that Duke JA recorded 39 types of action (clinical effects) described for the rhizomes of sanguinaria, and in table. 4 presents 119 indications for the use of drugs from this raw material with links to primary sources.

Generalized information (according to [54]) on the dosage of sanguinaria rhizomes and remedies from them are presented in table. 5.

Table 4

Indications for the use of Canadian sanguinaria (according to [54])

P / p No.	Indications for use in alphabetical order	Evidence base (by [54]), see note to table. 3
1	Adenopathy	1; CRC; Fnf
2	Alcoholism	f; CRC
3	Angina	f; CRC
4	Anemia (as well as chlorosis, a special form of anemia)	f; CRC; FEL (f; FEL)
5	Aphonia	f; CRC
6	Arthrosis	1; APA; COX; CRC
7	Asthma	f; CAN; CRC; FEL; HH3
eight	Bacterial infections	1; APA
nine	Insomnia	f; CRC
ten	Blepharosis	F; CRC
eleven	Diseases of the gallbladder and problems with bile secretion	f; DEM
12	Alzheimer's disease	1 COX; FNF; HH3
13	Pain	1; CRC; DEM; APA
fourteen	Sore throat	1; APA; CRC; FEL
15	Chest pain	f; CRC
16	Stomach ache	f; DE
17	Ear pain	f; CRC
eighteen	Fermentation in the stomach and intestines, defeat by yeast fungi	1; HH3
19	Bronchitis	1; CAN; CRC; HH3
twenty	Typhoid fever	f; CRC
21	Vaginitis	1; CRC; Fnf
22	Sexually transmitted diseases	f; CRC
23	Inflammation	1; APA; FEL; HH3
24	Inflammation of the mucous membranes, in the original - mucositis	f; FEL
25	Halitosis, bad breath	1; APA
26	Gastritis	f; CRC; FEL
27	Haemorrhoids	f; CRC; DEM
28	Hepatosis	f; CRC; DEM
29	Gingivitis	1; APA; PH2
thirty	Helminthic invasions	f; CRC; DEM
31	Glossitis	f; CRC
32	Deafness	f; CRC
33	Headache	f; CEB; CRC; FEL
34	Gonorrhea	f; DEM

35	Fungus and fungal diseases	f; CEB; FEL
36	Flu	F; CRC
37	Moronity	f; DEM; FEL
38	Dermatoses	f; FEL
39	Diarrhea	f; DEM
40	Dysentery	1; CRC; FEL; Fnf
41	Dysmenorrhea	F; CRC; DEM; HH3
42	Dyspepsia	f; CRC; DEM; FEL
43	Diphtheria	f; CRC
44	Duodenitis	f; FEL
45	Water retention in the body, edema	f; CEB; CRC
46	Constipation	f; CRC; DEM
47	Toothache	1; CRC
48	Plaque and tartar	1; CRC
49	Impotence	f; FEL
50	Infectious diseases, in the original - infections	f; HH3
51	Hysteria	f; FEL
52	Candidiasis (a type of mycosis)	f; HH3
53	Cardiopathy	f: DEM
54	Catarrh, inflammation	f; CRC; DEM; FEL
55	Cough	f; APA; CRC; DEM
56	Keratosis	f; CRC
57	Whooping cough	f; CEB; CRC; FEL
58	Congestion (congestion, congestion, blood congestion, congestion)	f; APA
59	Bleeding	f; DEM
60	Hemoptysis - originally hemoptysis - coughing up sputum with blood from the larynx, bronchi or lungs	f; CRC; DEM
61	Croup, obstructive laryngitis	1; CAN; CRC; DEM; FEL
62	Laryngitis	f; CRC; FEL; HH3
63	Fever	f; APA; CEB; CRC
64	Melanoma	1; HOX
65	Flatulence	f; DEM
66	Migraine	f; CRC
67	Mycosis	1; APA; FEL
68	Runny nose	f; CEB; DEM
69	Neuralgia	f; CRC
70	Nervousness	f; CRC
71	Fainting	f; DEM
72	Burn	f; CRC; DEM
73	Tumors	1; HH3
74	Tumors are malignant	1; APA; COX; CRC FNF
75	Swelling, swelling	1; HH3
76	Edema	f; CEB; CRC
77	Ophthalmia (a term used to denote a number of eye diseases, different in origin and clinical course. The term is also used to characterize the eye's response to intense light sources)	f; CRC
78	Felon	f; CRC
79	Periodontal disease	1; CRC
80	Peridontitis	1; FNF; JAD
81	Pneumonia	f; CRC; FEL
82	Gout	f; CRC
83	Polyps	1; CAN; CEB; DEM; HOX
84	Seizures	f; DEM
85	Tides	f; CRC
86	Cold	f; APA; CRC; DEM

87	Pulmonosis	f; CEB; DEM
88	Cancer	1; APA; COX; HOX; CRC FNF
89	Mammary cancer	1; CRC; JLH
90	Ear cancer	1; CRC; JLH
91	Cancer of the nose	1; CRC; JLH
92	Skin cancer	1; COX; CRC; JLH
93	Uterine cancer	1; CRC; JLH
94	Wounds and wound infections	F; DEM
95	Vomit	F; DEM
96	Rheumatism	f; APA; CRC DEM
97	Respirosis (lung disease of any etiology)	f; CRC
98	Rhinopathy (original - rhinosis)	f; CRC; HH3
99	Syphilis	f; CRC; DEM; FEL
100	Salmonellosis	1; HH3
101	Scarlet fever	f; CRC; FEL
102	Scrofula - mycobacterial cervical lymphadenitis	f; FEL
103	Condition after childbirth	f; CRC
104	Spermatorrhoea	F; FEL
105	Staphylococcus	1; HH3
106	Streptococcus	1; HH3
107	Ringworm	f; FEL
108	Convulsions	f; CAN; DEM
109	Nausea	F; DEM
110	Tracheitis	f; FEL
111	Tuberculosis	f; FEL; CEB; CRC; DEM
112	Chronic urethritis	f; CRC
113	Pharyngitis	1; CAN; CRC; FNF; HH3
114	Frigidity	f; CRC
115	Noise in ears	f; CRC
116	Eczema	f; CRC; FEL
117	Enteritis	f; DEM
118	Escherichiosis, in the original - Escherichia coli	1; HH3
119	Ulcers	f; DEM

Table 5

Dosing of drugs
and traditional remedies from sanguinaria (according to [54])

No. p / p	Part of a plant or dosage form (LF)	Dosage	Qty receptions per day	Application	A source (see notes to table 3)
1	Rhizomes, in different LF	0.06-0.50 g	3	By therapeutic indications (tab. 4)	CAN
2	Also	2.0 g	3	As emetic	CAN
3	Also	from 1 g		May be violent vomiting	AHP
4	Rhizomes, dried, in powder	0.5 g	Not indicated	By therapeutic indications (tab. 4)	PNC
5	Rhizome extract liquid 1: 1 in 60% ethanol	0.06-0.3 ml	3	By therapeutic indications (tab. 4)	CAN

6	Also	2.0 ml	3	As emetic	CAN
7	Rhizome extract liquid	0.5-1.5 ml	Not indicated	By therapeutic indications (tab. 4)	PNC
eight	Tincture 1: 5 in 60% ethanol	0.3-2.0 ml	3	By therapeutic indications (tab. 4)	CAN
nine	Tincture of rhizomes (without concentration indications ethanol and ratios "Raw material: extractant")	2.0-8.0 ml	Not indicated	By therapeutic indications (tab. 4)	PNC
ten	Also	8 ml	3	By therapeutic indications (tab. 4)	CAN
eleven	Dry rhizome extract	0.3-0.5 g	Not indicated	By therapeutic indications (tab. 4)	PNC
12	Preparations (without specifying specific DF)	from 0.03 g	Not indicated	As a consequence individual sensitivity	PHR

Thus, the experience of traditional use and evaluation of the results of modern experimental studies of sanguinaria allow us to conclude that further study of this plant is necessary, both as a source of individual alkaloid compounds and as a complex extract from rhizomes [43].

4. Assessment of the safety of the Canadian sanguinaria:

potential toxicity, contraindications for use, side effectsAccording to experts, most patients believe that natural remedies and herbal remedies are significantly safer than synthetic pharmaceuticals [43, 70]. Approximately 45% of the population in Western countries used complementary and alternative medicine (CAM) for at least 12 months [88].

In this regard, in many countries of the world there are serious concerns about the lack of state regulatory control over the natural medicine sector in terms of supervision of the quality of herbal remedies and patient safety [21]. Natural remedies in these countries can be sold without prior proof of their safety and efficacy, and the government authorities responsible for supervision in this area must prove the toxicity of an agent and / or the danger of its use before it can be removed from the market [25]. In particular, work [41] provides a review of the safety of OTC drugs of traditional Chinese medicine, showing that of the 26 products studied, 92% were contaminated with heavy metals or pharmaceutical agents.

4.1. Safety Data Sheets Sanguinaria canadensis

Despite the fact that sanguinaria rhizomes are part of a number of multicomponent cough preparations, due to the presence of a fairly toxic alkaloid sanguinarine in them, the US Food and Drug Administration (FDA) characterizedSanguinaria canadensis as an unsafe plant [54, 178]. However, these data cannot be considered fully substantiated, since, according to the PDR for Herbal Medicines (2007), with the proper use of the prescribed therapeutic dosesSanguinaria canadensis health hazard or side effectsthere are no effects from the use of drugs from this plant [166].

4.2. Potential toxicity

According to PDR for Herbal Medicines (2007), pure alkaloids initially act like a drug, causing severe spasms, accompanied by local paralysis of sensory nerve endings [166], at the same time, this statement has been shown to be true for the aerial organs of sanguinaria, but not for rhizomes [1].

According to the classic compilation monographs and reference books by Duke JA [54], the plant belongs to class 2 (B) in terms of its toxicity: in large doses (Table 5) it can cause nausea and vomiting.

According to Commission E (KOM) plant evidence and included in the 2nd edition of the PDR for Herbal Medicines (Dangerous and / or Side Effects for Appropriate Therapeutic Dosages) [80], an overdose of Sanguinaria rhizomes in any dosage form can cause colic, diarrhea, enterosis, vomiting and even collapse [54].

Studies carried out at the Faculty of Medicine of the Institute of Medicinal Chemistry and Biochemistry at Palacký University (Czech Republic) showed that the average daily oral dose of sanguinaria alkaloids up to 5 mg per 1 kg of animal body weight was found to be safe [115]. The studies were carried out in connection with the presence of unconfirmed information on the genotoxicity and hepatotoxicity of sanguinaria alkaloids, in particular sanguinarine and chelerythrine. In an experiment, a 3: 1 mixture of these alkaloids was added to pig feed for 90 days. Then they were quantified in tissues. The highest accumulation of alkaloids (and their concentration) was found in the gums (0.55 μg / g) and liver (0.15 μg / g), while no alkaloids were found in the muscles. Plasma sanguinarine levels reached 0.11 μg / ml. Hematological results,

None of the clinical studies with oral administration of sanguinarine from sanguinaria have also reported hepatotoxicity [54]. The claims about the glaucomogenous activity of sanguinarine have also been refuted. It has been shown that this type of toxicity, previously attributed to sanguinarine, should be attributed to oilsAlfaroa mexicana (Family Juglandaceae - Nut) [54].

As for the external use of sanguinaria, according to [156], mouth rinses and toothpastes containing Sanguinaria extracts or pure sanguinarine, all the same, may have practical clinical significance in oral hygiene due to their proven low toxicity.

Allergenicity. Clinic patchtests (a method used to determine whether a particular substance causes allergic skin inflammation) have shown that sanguinarine is not irritating or sensitizing. Animal studies have also shown that this alkaloid is non-allergenic and does not exhibit anaphylactic potential [54]. However, according to the expert opinion, it is best to avoid the use of sanguinaria drugs during pregnancy and lactation [54].

Cytotoxicity. While the cellular cytotoxicity of individual alkaloids was sufficientwell studied (section 2), the cytotoxicity of polyalkaloid extracts has received minimal coverage in scientific periodicals. Although the relevance of these studies is undoubted, since, for example, the study of the antimicrobial effect of sanguinaria rhizomes showed that the natural combination of alkaloids
S. Canadensis possesses in 4 times more effective against H. pylori versus individualalkaloids [131]. The same combination of alkaloids showed a more effective destructionTrypanosoma brucei (before 10 times) [117].

The cytotoxic effect of the total alkaloid fraction obtained from the herb of celandine(Chelidonium majus), has been evaluated against murine fibroblast cell lines NIH / 3T3, mouse melanoma B16F10, and human breast cancer MCF7. The alkaloid fraction contained 3.3 μg / ml of each of the alkaloids - sanguinarine, protopine, alcryptopine, chelidonine and stylopin. The study revealed the predominant cytotoxicity of the mixture of alkaloids against melanoma with 45% cell viability after 40 minutes, while the viability of normal cells was 75% [118].

Unfortunately, work [118] does not report on the study of the cytotoxicity of individual alkaloids in comparison with the cytotoxicity of the indicated mixture, which does not allow assessing the presence of synergism of individual ingredients in the alkaloid mixture. It was noted only that almost twice as many alkaloids penetrated into normal cells as compared to tumor cells. And, despite this, normal cells experienced a lesser cytotoxic effect, apparently due to the predominant penetration of alcryptopine and stylopin into them. In contrast, cancer cell lines have shown preferential penetration and accumulation of sanguinarine and chelidonine [118].

Potential carcinogenic and mutagenic risks. Clinical concern of some

specialists, in addition to cytotoxicity, causes a carcinogenic and / or mutagenic risk from the use of herbal therapeutic agents from S. canadensis. In particular, it has been shown that the means formouthwash based S. canadensis cause leukoplakia (precancerous condition) [43].

It has also been shown that exposure to potentially genotoxic alkaloids can initiate or promote tumor development, for example, skin cancer often develops in the area of genetically damaged cells [26]. In particular, it was revealed that if the cancer cells were not destroyed by the "black ointment" (section 3), they can be subjected to further genetic damage under its influence. That is, "black ointment" can make them more aggressive and at the same time resistant to treatment [26, 43].

At the same time, according to [54] with reference to [156] and other sources (Table 5), the carcinogenic potential of drugs and products from sanguinaria was refuted, and there is no reliable documentary data on the toxicity or side effects of sanguinaria in therapeutic doses.

The same data have been confirmed in experimental studies. Taking into account that the formation of DNA adducts (the combination of any molecules with DNA) in the body often occurs under the influence of carcinogens, their metabolites, or is provoked by carcinogens, a corresponding study was carried out at the Faculty of Medicine of the Institute of Medicinal Chemistry and Biochemistry of Palacký University (Czech Republic) in a group of experimental animals described in section 4.2 [115]. No DNA adducts with sanguinarine and chelerythrine were found in pig liver 90 days after the beginning of alkaloids administration. Also, no symptoms were observed associated with the epidemic syndrome of dropsy, which is often attributed to sanguinarine [115].

Studies investigating the carcinogenic potential of pure sanguinarine have yielded conflicting results [10]. In female Swiss albino mice exposed to 1,3 dimethylbutylamine (DMBA) as an initiator when combined with a single application with sanguinarine (concentration 4.5 μM), there was no increase in the rate of tumor development, compared with the use of only the substance DMBA without sanguinarine [10] ...

In the same experiment, another group of mice was injected with DMBA, and twice a week - topically applied 1.5 μM sanguinarine for 25 weeks. In this group, an earlier onset of tumorigenesis and an increase in the average number of tumors per mouse from 5 (for the DMBA initiation group) to 7.07 (for the DMBA group followed by 25 weeks of sanguinarine use) were recorded. This result led the researchers to suggest that sanguinarine may act as a tumor promoter [10].

At the same time, section 2.7 describes an experimental study [6, 169, 226], which showed that by protecting cells damaged by ultraviolet light and reducing the inflammatory changes caused by ultraviolet light, sanguinarine can inhibit the development of cancer. According to experts, the opposite results obtained in the described studies in terms of potentiation of development and / or, on the contrary, protection against cancer, in various mouse models, require early clarification in further studies, especially given the fact that these drugs are currently actively used patients [43].

Some restrictions on the food use of sanguinaria dating back to 1997 are described. In particular, it is reported that Canadians do not consider it possible to allow sanguinaria rhizomes to be widely used for food in connection with the risks of glaucoma [141]. There are no supporting experimental and clinical data corresponding to this period of time (or more recent) in the scientific periodicals.

4.3. Contraindications

Sanguinaria preparations should not be used during pregnancy [165]. Commission E in Germany does not recommend the uncontrolled oral use of sanguinaria rhizomes as monotherapy due to the potential toxicity [24].

4.4. Adverse reactions and overdose

Drugs Sanguinaria canadensis emetic at doses higher 0.03 g (previously these properties were used for therapeutic purposes) [166]. Higher doses of the drug are highly irritating to the mucous membranes, both orally and topically [166]. Overdose can cause vomiting [24, 166], diarrhea, intestinal colic [166], loss of consciousness [24] and even collapse [166].

Overdose can lead to stomach burns, vomiting, dizziness, weakness, and loss of vision. Therefore, taking sanguinaria should be carried out under the supervision of a physician [50].

4.5. Precautions related

with the lack of domestic regulatory documents for raw materials

The dependence of the qualitative composition and quantitative content of biologically active substances in a plant on the conditions of its growth, the phase of harvesting and storage conditions of raw materials, climatic and other factors, well known in pharmacognosy, is also relevant for Canadian sanguinaria [43]. In particular, work [176] reports that natural variation of biologically active alkaloids in a producing plant can cause unpredictable clinical effects of S. canadensis extracts. For example, according to [20], raw materials (horses) collected in different geographic locations can demonstrate a significant change in the alkaloids profile, up to 15-fold differences in the concentration of sanguinarine.

Since in our country the plant is unofficial, methods of standardization and norms for the content of biologically active substances in raw materials have not been developed, and there is no regulatory documentation for it, the risk of toxic effects actually increases when trying to obtain drugs with a high concentration of active compounds to achieve the desired clinical effects. Consequently, for the development and further scientifically substantiated introduction of preparations and specialized food products based on the rhizomes of Canadian sanguinaria in the Russian Federation, the development of domestic regulatory documents is required.

Thus, despite the fact that today the spectrum of proven pharmacotherapeutic action of various S. canadensis alkaloids is quite wide (Section 2), there are works describing the cytotoxicity [48] of traditional medicinal agents (extracts) and their mutagenic risks [107] (see . also Section 4), does not yet allow making an unambiguous conclusion about the advisability of bringing these drugs to routine clinical use as monotherapy for a wide range of diseases, including neoplastic ones. Additional clinical studies are required both in terms of efficacy (for specific indications) and in terms of the safety of substances and preparations based on Canadian sanguinaria [43].

CONCLUSION

Our information-analytical study made it possible to establish (taking into account the opinion of international experts [43, 108]) that the creation of modern multicomponent formulations based on sanguinaria extract (based on the principles of kinetic synergism and antagonism), acting in the body simultaneously and consistently for several purposes, can be considered reasonable and scientifically sound. The creation of regulatory documents for the raw materials of sanguinaria imported or cultivated in the Russian Federation is a prerequisite for the introduction of drugs from it into domestic medico-pharmaceutical practice.

CONCLUSIONS

1. An information-analytical study of the spectrum of biological activity, experience traditional use and modern ideas about the ways of using canadian sanguinaria(Sanguinaria Canadensis L.) in modern medicinepharmaceutical practice.

2. It is shown that the accumulated ethnobotanical and ethnopharmacological material caused significant interest in the experimental and clinical study of sanguinaria on the part of individual researchers and entire scientific teams.

3. Based on the analysis of published research results, antitumor, anti-inflammatory, antimicrobial, antiviral, antiparasitic, antidiabetic action of rhizome extracts and individual alkaloids isolated from this plant.

4. Revealed works describing the mechanisms of action of sanguinarine and chelerythrine on cancer the cell, as well as the processes that determine the antitumor effect of sanguinaria alkaloids, their effect on the activity of the stomach and intestines, heart and blood vessels, as well as on insulin resistance.

5. The study made it possible to establish that the rhizomes of sanguinaria can be a promising source of modern domestic medicines and / or phytonutrients for the creation of dietary supplements for food and specialized food products.

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