DOI: https://doi.org/10.17816/KMJ634368

Possibilities of using secondary plant metabolites as antitumor agents

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ABSTRACT

The review summarized the literature data of recent years on the antitumor effect of secondary plant metabolites, as well as their immunotropic and anti-inflammatory effects as components of the antitumor response. The biological basis for the action of secondary plant metabolites was characterized in the form of influence on potential targets: transcription factors, signaling pathways and receptors responsible for proliferation and apoptosis. The ways of increasing the bioavailability of secondary plant metabolites to enhance the effectiveness and possibility of their medicinal use were considered, the effects of berberine, curcumin and their derivatives were described. The search for scientific publications was conducted in foreign (PubMed) and domestic (eLibrary) electronic libraries. It was found that the multiplicity of molecular targets of secondary plant metabolites and the pleiotropy of their effects suggest the possibility of their use for the regulation of various processes in tumor and normal cells. There was a connection between the antitumor effect of secondary plant metabolites and their anti-inflammatory and immunomodulatory action. However, a significant limitation of their use was the fact that most studies were conducted on cell cultures, which was insufficient to judge the antitumor effect. Clinical trials were few and their results were contradictory. In addition, a certain contradiction has been noted between the idea of a more effective action when using a pure substance or a complex composition of various plant components. An important problem was the low bioavailability of most secondary plant metabolites, for which various methods have been proposed. Despite the long history of phytotherapy in oncology, the development of new derivatives of secondary plant metabolites with high water solubility remains relevant, including modified molecules of known secondary plant metabolites and the search for new ones with unexplored biological activity. Modern methods of chemical synthesis and delivery systems of derivatives of secondary plant metabolites, as well as the study of their effects in model experiments, seem to be promising scientific directions for the creation of new drugs with antitumor activity.

Keywords: medicinal plants; antitumor action; immunotropic action; secondary plant metabolites; berberine; curcumin.

To cite this article:
Zlatnik EYu, Sagakyants AB, Nepomnyaschaya EM, Zakharova NA, Ulianova YuV. Possibilities of using secondary plant metabolites as antitumor agents. *Kazan Medical Journal.* 2024;105(5):813–824. doi: https://doi.org/10.17816/KMJ634368

Received: 18.07.2024 **Accepted:** 02.09.2024 **Published:** 02.10.2024

DOI: https://doi.org/10.17816/KMJ634368
УДК 616-006.6: 577.127: 577.13: 577.175.19: 577.29

Возможности применения вторичных метаболитов растений как противоопухолевых средств

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АННОТАЦИЯ

В обзоре обобщены данные литературы последних лет о противоопухолевом действии вторичных метаболитов растений, а также их иммунотропном и противовоспалительном действии как компонентах противоопухолевого ответа. Охарактеризованы биологические основы действия вторичных метаболитов растений в виде влияния на потенциальные мишени: транскрипционные факторы, сигнальные пути и рецепторы, ответственные за пролиферацию и апоптоз. Рассмотрены пути повышения биодоступности вторичных метаболитов растений для усиления эффективности и возможности их медикаментозного применения, описаны эффекты берберина, куркумина и их производных. Поиск научных публикаций проведён в зарубежных (PubMed) и отечественных (eLibrary) электронных библиотеках. Установлено, что множественность молекулярных мишеней вторичных метаболитов растений и плейотропность их эффектов предполагают возможность их применения для регуляции различных процессов в опухолевых и нормальных клетках. Прослеживается связь между противоопухолевым эффектом вторичных метаболитов растений и их противовоспалительным и иммуномодулирующим действием. Однако существенным ограничением их применения становится то обстоятельство, что большинство исследований проведено на культурах клеток, что недостаточно для суждения о противоопухолевом действии. Клинические испытания немногочисленны, и результаты их противоречивы. Кроме того, отмечено определённое противоречие между представлением о более эффективном действии при использовании чистого вещества или сложной композиции разнообразных растительных компонентов. Важная проблема — низкая биодоступность большинства вторичных метаболитов растений, для повышения которой предложены различные способы. Несмотря на давнюю историю фитотерапии в онкологии, остаётся актуальной разработка новых производных вторичных метаболитов растений, обладающих высокой водорастворимостью, включая модифицированные молекулы известных вторичных метаболитов растений и поиск новых, с неисследованной биологической активностью. Современные методы химического синтеза и систем доставки производных вторичных метаболитов растений, а также исследование их эффектов в модельных экспериментах представляются перспективными научными направлениями для создания новых лекарственных препаратов с противоопухолевой активностью.

Ключевые слова: лекарственные растения; противоопухолевое действие; иммунотропное действие; вторичные метаболиты растений; берберин; куркумин.

Как цитировать:
Златник Е.Ю., Сагакянц А.Б., Непомнящая Е.М., Захарова Н.А., Ульянова Ю.В. Возможности применения вторичных метаболитов растений как противоопухолевых средств // Казанский медицинский журнал. 2024. Т. 105, № 5. С. 813–824. doi: https://doi.org/10.17816/KMJ634368

Рукопись получена: 18.07.2024 **Рукопись одобрена:** 02.09.2024 **Опубликована:** 02.10.2024

Phytotherapy for the treatment of various diseases has been known since ancient times, and interest in it remains up to this day. The development of technologies allows determining various components of plants and characterizing their biological activity, which indicates their potential use in medicine [1]. Primary and secondary metabolites and plant hormones are distinguished among plant metabolites [2].

Secondary plant metabolites (SPM) attract the interest of researchers [3]. This term was first proposed by German biologist Albrecht Kossel in 1891. SPM are small molecules with a molecular weight of <3000 Da [4]. They are typically divided into several main large groups [5]:

– Isoprenoid, also called terpenoids, include over 40,000 structures and form the largest class of all known SPM. They represent a class of hydrocarbons, which are products of biosynthesis with the general formula $(C_5H_8)n$ and with a carbon skeleton that is a derivative of isoprene $CH_2=C(CH_3)–CH=CH_2$.

– Alkaloids have a heterocyclic structure, contain a nitrogen molecule in the heterocycle, and include approximately 21,000 compounds.

– Phenolic compounds are aromatic compounds with a benzene ring containing at least one hydroxyl group.

The biological activity of SPM is due to their chemical aspects, because of which they are able to enter into reactions, undergoing methylation, acylation, glycosylation, hydroxylation, and desaturation in the presence of various enzymes. Their main function is protection against biological and nonbiological adverse effects [6] — the one that makes them similar toto the immune system of animals, although SPM have a different nature and are not pathogen-specific. The biological activity of SPM should be manifested in relation to animal and human cells, as a result of which they are applied in medicine, and this search continues [7].

BIOLOGICAL JUSTIFICATION OF THE USE OF SECONDARY PLANT METABOLITES IN ONCOLOGY

The derivatives of various plants are used in medicine as analgesics (morphine and codeine), muscle relaxants (tubocurarine) and antimalarial, antipyretic, and sedative agents. Some SPM are used in oncology, including the antitumor antibiotics actinomycin D, anthracyclines (doxorubicin, epirubicin, and daunorubicin), mitotic poisons (mitomycin C, bleomycin, colchicine, and colchamine), vincristine, vinblastine, and taxol [8].

The search in this direction is developing. Thus, reviews summarizing the potential for the antitumor action of plant components and their role in modern tumor therapy have been published, including studies of SPM targets and the possibilities of integrating phytochemicals and phytotherapy into standard cancer therapy [9] based on an analysis of the effect of SPM on the PI3K/Akt/mTOR, Bax/Bcl-2/caspases, and NF-κB/Nrf2 signaling pathways that mediate apoptosis and proliferation and are significant for tumor growth [10].

SPM are studied as part of plant extracts, which serve as a multicomponent mixture of various substances, and in the form of purified or synthetic substances with certain structural and functional characteristics; their effect on tumor cells has been revealed in both cases. For example, MTT test[1] showed that aqueous solutions of *Sansevieria cylindrica* leaf and rhizome extracts reduced the survival rate of human lung adenocarcinoma A549 cells by two times. This allows considering these extracts as potential sources of active metabolites capable of inhibiting tumor cell growth [11], although it remains unclear which specific SPM produced the effect. Another study revealed the antitumor effect of rice callus culture by its anti-inflammatory and cytotoxic activity [12].

However, some studies presented alternative opinions [13], such as that SPM contained in natural compounds may be antagonists for each other and that pure substances may exhibit a more pronounced effect.

A crucial argument in favor of using purified or synthetic SPM is the nonstandard nature of natural plant materials, as the quantity and quality of natural SPM in plants depends on environmental factors [14], in particular soil composition. The present study demonstrates that SPM obtained from plants grown in soils with an increased content of certain metals can exhibit an effect opposite to that expected.

When studying the antitumor effects of individual groups of SPM, for example, flavonoids, which are part of the group of phenolic compounds, their effect on metastatic spreading was revealed, wherein inhibition was noted in in vitro models in the form of an effect on key signaling pathways responsible for migration, invasion, epithelial–mesenchymal transition, and regulation of molecules such as MMPs, uPA/uPAR, and TGF-β. Additionally, flavonoids modulate the expression of genes that control tumor progression mediated by chronic inflammation [15].

In vitro, the MTT test revealed the activity of the flavonoid extract against melanoma cell lines [16], and in vivo preclinical studies have shown that the flavonoid apigenin, which is found in several vegetables and fruits, inhibits mouse melanoma metastasis to the lungs and the growth of breast cancer xenografts [17]. Another flavonoid, quercetin, inhibits migration of prostate cancer tumor stem cells with the $CD44^+CD133^+$ phenotype and spheroid formation [18].

Several alkaloids have a similar effect. Among them, colchicine, an inhibitor of microtubules and mitosis, has long been known and is the most well-studied; however, troponoids also have similar activity, which, in addition, damages the mitochondria [19], which allows considering them as antitumor substances. In vitro and in vivo experiments demonstrated a higher (18-fold) antitumor activity of the 2-quinolyl-1,3-tropolone derivative compared with the cytostatic cisplatin and its ability to significantly inhibit (65%–75%) the growth

[1] MTT: methyl thiazolyl tetrazolium.

of subcutaneous xenografts of the human lung cancer culture A-549 in immunodeficient mice [20].

Tubulin-binding agents cause cell-cycle dysregulation in the G2/M phase and cell division synchronization. Studies have described the ability of an indole-containing inhibitor of tubulin polymerization to bind to the colchicine-binding site in the region between the α- and β-subunits of its heterodimer [21]. Among the developed and synthesized trans-indolyl-3-acrylamide derivatives that bind to the colchicine site, the most active ones that cause cell cycle arrest in Huh7 hepatocellular carcinoma cells were selected [22].

Additionally, indole alkaloids regulate the autophagy process by influencing the PI3K/Akt/mTOR, MAPK, ROS, Beclin-1, and other signaling pathways; however, a review published in 2022 and world literature data for 2009–2021 were unable to establish to what extent this is associated with the described antitumor properties of indole derivatives, which are plant and/or bacterial products, as the role of autophagy has an ambiguous interpretation, and it is considered either as a precursor to cell death by apoptosis or passive witness to this event [23].

However, an imbalance of endogenous indole metabolites in patients with lung cancer has been described in the literature, and its features have been found to be associated with the effect of immunotherapy and are considered as prognostically significant [24].

In a meta-analysis, Li et al. [25] summarized data on the properties of monoterpene indole alkaloids (corynanthe) with different chemical structures and various biological activities, among which the analgesic, antiparasitic, antibacterial, and antiviral effects have been studied in detail. Thus, the activity of one of the substances in this group (hirsutine) was 10–20 times greater than the effect of ribavirin against influenza A virus in vitro, whereas another substance (normavacurin-21-1) exhibited an antibacterial effect against enterococci, comparable to the effect of cefotaxime.

Many derivatives of these alkaloids, similar to other SPM, have an anti-inflammatory effect, suppressing lipopolysaccharide-induced nitric oxide synthesis in macrophages. Only one study mentioned the NF-κB-mediated inhibitory effect of one of them on the HeLa tumor cell culture [26]. These alkaloids have a tetra- or pentacyclic structure, which is stereochemically different owing to the presence of several chiral centers, which complicates their synthesis and indicates uncertainty in the relationship between their chemical structure and biological activity. The authors of this meta-analysis believe that clarification of the latter will serve as a basis for the development of new pharmaceuticals.

The literature data presents some divergence in the views on the effectiveness of compositions and complex extracts with a difficult-to-control composition and individual biologically active substances isolated or synthesized based on natural SPM. Among the latter, special attention is paid to the alkaloid berberine and the polyphenol curcumin, although they are often used in extracts and compositions [27, 28].

ANTITUMOR PROPERTIES OF BERBERINE AND ITS DERIVATIVES

Berberine as a separate substance is capable of inducing tumor cell differentiation by inhibiting the crucial mechanisms of malignant growth, namely, tumor stem cells and epithelial–mesenchymal transition [29, 30], and increasing the sensitivity of tumor cells to radiation [31].

Induction of apoptosis and cell-cycle arrest under the action of berberine has been noted in several tumor cell lines [32]. In vitro cell growth models have revealed the damaging effect of berberine on esophageal cancer cells and inhibition of migration and proliferation of colorectal cancer cells [33].

According to the literature, such activity is mediated by the effect of berberine on targets and signaling pathways responsible for tumor growth. Thus, the mechanisms of the proapoptotic effect of berberine include inhibition of MDM2-mediated autophagy in leukemia cells [34], Akt pathway suppression in breast cancer cells [35], angiogenesis inhibition in glioblastoma xenografts [36], and action on the factors and signaling pathways NF-κB, HIF1A, and NFE2L2/AP-1 in cervical cancer cells [37], which is partly confirmed by the cytotoxic effect on HeLa cell culture [38]. These and many other transcription factors and signaling pathways can be considered targets of berberine.

Chinese authors, who are most intensively advancing these studies, have proposed synthetic derivatives of berberine as antitumor agents [39]. However, despite the promising potential of its clinical application, the authors characterize the potential only as a possible one [40].

The combined use of SPM and chemotherapy drugs to enhance antitumor effect has been proposed, as in vitro and in vivo experiments have shown synergism between berberine and erlotinib in the form of increased inhibitory effect on pEGFR and pAKT, expression of cyclin D and Bcl-2 compared to monotherapy with berberine or erlotinib, which is also manifested in a decrease in the volume of transplanted tumors in athymic mice [41].

Conversely, the combined use of berberine and bosutinib [42] or cyclosporine [43] affects the concentration of these drugs in the blood and seems undesirable owing to possible toxicity. Additionally, the activity of berberine, similar to several other drugs, is affected by the composition of the intestinal microbiota, which normally promotes its transformation into an easily absorbed form [44]. However, in pathological conditions, this effect remains to be studied. According to Chinese studies, berberine influences the course of many diseases through its effect on the microbiota [45].

ANTITUMOR PROPERTIES OF CURCUMIN AND ITS DERIVATIVES

The antitumor effect of the polyphenol curcumin is presented in some studies as a result of its anti-inflammatory and immunomodulatory activity, because of which it affects

proliferation, apoptosis, angiogenesis, and metastasis [46] through its effect on the molecular targets COX-2, ROS, NF-κB, JNK, and STAT3 [47]. The effect of curcumin on autophagy has been noted; however, as in the case of other SPM, it appears controversial because of the uncertain role of this process in tumor growth [48].

A review [49] provided data on the fact that curcumin suppresses the growth of U87MG and U373MG glioblastoma cells by inducing autophagy through negative AKT/mTOR kinase regulation, ERK1/2 activation, and increased LC-3 II expression. However, in another study performed on a rat C6 glioma model, curcumin caused a decrease in the glioma volume, which is not associated with induction but with inhibition of autophagy.

A 2024 review [50] focused on a more detailed description of the molecular targets and processes wherein curcumin acts on. Previous studies specified that targets present in tumor cells (CDK2, CK2α, GSK-3β, DYRK2, EGFR, AXL receptor, FR-β, DHFR, Topo I and II, and NF-κB) and in cells involved in the development of chronic inflammation that promotes tumor growth, recurrence, and chemoresistance. The review summarizes the effects of curcumin and its analogues on many tumor cell cultures, particularly the induction of apoptosis, cell cycle arrest, proteasome inhibition, decreased cell invasion capacity, and metabolic process suppression under the influence of curcumin in vitro.

Clinical results are less representative. The author cites five studies, two of which were performed on patients with benign, albeit precancerous, processes, namely, familial intestinal polyposis and leukoplakia of the oral mucosa. The results of two more studies (chronic myeloid leukemia and multiple myeloma) indicated improving only laboratory parameters, and although these studies were published over 10 years ago, this direction has not yet been developed. Only in cases of prostate cancer, the inclusion of curcumin in the treatment regimen contributed to increased clinically expressed responses to docetaxel chemotherapy [51].

Moreover, other studies emphasized that although a positive effect of curcumin has been revealed in tumors of the lung, mammary and prostate glands, liver, and colon and in lymphoproliferative diseases, it is limited by the low bioavailability of the substance, and the clinical results should be confirmed in larger cohorts [52, 53].

As in the case of berberine, curcumin has been shown to exhibit synergism with cytostatic agents, for example, with docetaxel in prostate cancer and with 5-fluorouracil in colorectal cancer, and its antimetastatic effect has been shown, which is mediated through a cascade including miR-34a/b/c and the ROS/KEAP1/NRF2 signaling pathway [54].

There are isolated studies on the combined effect of pure berberine and curcumin on various tumor cell cultures. Synergism of the substances was noted in the form of a significant increase in cell death [55].

IMMUNOTROPIC AND ANTI-INFLAMMATORY EFFECTS OF SECONDARY PLANT METABOLITES AS A COMPONENT OF THE ANTITUMOR EFFECT

In many studies, antitumor effect was considered in the context of the anti-inflammatory and immunotropic effects established for most of the studied SPM.

Thus, a 2021 review summarized long-term data on the assessment of the immunotropic effect of plant components, considering their effects as immunostimulants, immunosuppressants, and immunoadjuvants and the dependence of their effect on the age and sex of patients, environmental conditions, stress, bad habits, etc. [56]. The advantages and disadvantages of natural and synthetic plant metabolites were characterized, and it was revealed that alkaloids play a major role in the correction of immune system functions by influencing cytokine synthesis and the balance of T-lymphocyte subpopulations, although a similar effect has been found in polyphenols (e.g., flavonoids, polysaccharides, lectins, etc.). The authors believed that SPM have potential for clinical use for immunomodulation in autoimmune diseases; however, oncological pathology was not mentioned in this study.

Some immunomodulatory effects of alkaloids are specified in the study by Jantan et al. [57], wherein the effect of an alkaloid (VF-1) isolated from *Voacanga foetida* in different concentrations on RAW 264.7 macrophages in vitro was shown and their safety was established with a decrease in interleukin (IL)-6 production. Jantan et al. believe that the use of this alkaloid can become a new strategy in inflammatory disease treatment. Considering the role of IL-6 in tumor growth and progression [58], the substance may also have an antitumor effect.

An analysis of 150 plant components used as immunomodulators showed that approximately 40% are plants from the genus *Asteraceae*, of which *Echinacea purpurea* is well known [59]. The authors pointed out that despite the high immunomodulatory activity of many polyphenols, terpenoids, and alkaloids, only eight plant products have undergone clinical trials and are available on the pharmaceutical market. These include six immunosuppressants (resveratrol, colchicine, capsaicin , quercetin, epigallocatechin-3-gallate, and andrographolide) and two immunostimulants (curcumin, and genistein).

The immunomodulatory effect of several SPM is associated with an anti-inflammatory effect, the main mechanism of which is the effect on the formation of cytokines and signaling pathways responsible for iNOS, PGE, and COX-2 synthesis. However, despite the ability of curcumin to inhibit the production of pro-inflammatory cytokines (tumor necrosis factor α, IL-1, IL-6, and IL-12) by stimulated monocytes, macrophages, dendritic cells, and spleen lymphocytes [60], its inclusion in

the treatment of patients with various inflammatory diseases does not affect the level of pro-inflammatory cytokines such as IL-6 and IL-8, although it leads to a decrease in the levels of tumor necrosis factor α and IL-1 [61].

Despite the properties of curcumin, including its effect on the immune system, which should be implemented in its antitumor effect (inhibition of the synthesis of NO, iNOS, COX-2, NKkB, and pro-inflammatory cytokines), and individual successes in its use in experimental models and in the clinic, further research is required to recognize it as an antitumor agent [62].

A similar conclusion was made in a later study, which emphasized the various properties of curcumin (i.e., antibacterial, antiasthmatic, antinociceptive, cytotoxic activity, and the ability to inhibit mitogen-induced lymphocyte proliferation) [63].

Moreover, berberine has been shown to reduce the formation of cytokines produced by macrophages, primarily IL-6 [64]. Additionally, its healing effect in inflammatory bowel diseases has been noted, which is implemented through inhibition of the synthesis of pro-inflammatory cytokines (tumor necrosis factor α, interferon γ, and IL-17) by intestinal macrophages by suppressing the MAPK and NF-κB pathways and fusion on the polarization of macrophages through activation of the AKT1/SOCS1 pathway [65]. The same authors indicated that in experimental colitis, the effect of berberine on the response mediated by Th1 and Th17 lymphocytes is associated with positive changes in the intestinal microbiota. This work does not concern malignant tumors; however, the cells, molecules, and signaling pathways mentioned may play a role in carcinogenesis.

POSSIBLE CAUSES OF INSUFFICIENT ANTITUMOR EFFICIENCY OF SECONDARY PLANT METABOLITES

Several studies have shown the activity of SPM in cell cultures, far fewer sources address experimental models, and clinical use cases are rarely documented. This is because of the complexity of their use, as most SPM have low bioavailability and are poorly soluble in water. To ensure the effect with oral administration, absorption and metabolism of a substance, which should have high water or fat solubility, is critical. Parenteral administration involves the use of the active form of the substance or its metabolism in the blood serum, which is challenging owing to insufficient solubility. In this regard, one of the crucial issues is increasing the bioavailability of SPM, which is the focus of several developments presented in the literature.

In a study by Thomas et al. [66], technologies for increasing the content of biologically active components with antioxidant action were considered, including ultraviolet irradiation, extraction modes, and plant drying, and references were given to the possibility of increasing the bioavailability of phenolic SPM using various bioprocessing options, such as fermentation of plant materials, which leads to an increase in their solubility and thermal stability.

In their study, Cosme et al. [67] analyzed the factors influencing the bioavailability of polyphenols in food products. The role of microbiota in the fermentation of these SPM and the importance of their metabolism in the liver with the formation of biologically active forms were emphasized. An increase in bioavailability using delivery systems is proposed, for example, placing curcumin in chitosan nanocapsules or its use in the form of a nanospray. Furthermore, the authors considered the use of SPM as prodrugs activated in the gastrointestinal tract and the production of phytosomes, that is, phospholipid complexes with SPM, which impart lipophilicity, to be promising. An increase in the inhibitory effect of berberine on cytokine synthesis was obtained using its conjugate with erythrocytes [68].

The low solubility and absorption of berberine, its P-gp-mediated efflux from cells, and rapid clearance hinder the creation of the concentration in tissues necessary for the manifestation of its biological properties. Various strategies, summarized by Thomas et al. [66], were aimed at overcoming this. These strategies include the production of nanocapsules (including chitosan, as in the case of curcumin), nanocrystals, myceliated forms, liposomes, microemulsions, and microparticles, the use of which led to an increase in the serum concentration of berberine after its administration to animals.

An alternative approach considered was the development of synthetic derivatives and analogs of berberine, including isomerization or the addition of functional chemical groups, although the work indicates that, despite the higher activity of many analogues and derivatives of berberine compared to the original substance, it was not associated with their concentration in the blood and tissues.

CONCLUSION

Thus, an analysis of the literature in the field of searching for and developing SPM with antitumor and immunomodulatory action revealed the following:

– The majority of studies were conducted on cell cultures and not on tumor models reproduced in animals, and clinical trials were few. Their results were contradictory.

– The multiplicity of the molecular targets of SPM and pleiotropy of their effects indicates the possibility of their use to regulate various processes in tumor and normal cells.

– An associated between the antitumor effect of SPM and their anti-inflammatory and immunomodulatory action was noted; however, no studies have been conducted on the processes and interactions occurring in the tumor microenvironment when they are used.

– A contradiction has been revealed between the idea of a more effective action when using a pure substance and a complex composition of various plant components.

DOI: https://doi.org/10.17816/KMJ634368

– Despite the repeatedly described antitumor effect of various SPM, among which berberine and curcumin are especially often considered, the effect is limited by their low bioavailability, which is increased by various approaches.

– It seems promising to develop new SPM derivatives with high water solubility, including modified molecules of known SPM, and search for new ones with underinvestigated biological activity.

– The antitumor activity of these substances should be studied not only in the form of mono-agents but also in combination with chemo- and immunotherapy.

ADDITIONAL INFORMATION

Authors' contribution. E.Yu.Z. — conceptualization, formal analysis, writing — review and editing, supervision; A.B.S., N.A.Z., Yu.V.U. — methodology, validation, investigation, writing — original draft; E.M.N. — writing — review and editing, supervision.

Funding source. The study was carried out with the financial support of the state assignment "Search for natural and synthetic secondary plant metabolites with antitumor and immunocorrective properties in *in vitro* and *in vivo* models", registration number 124022100044-2 from 2024.

Competing interests. The authors declare no conflict of interest regarding the presented article.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Е.Ю.З. — концептуализация, анализ, редактирование рукописи, общее руководство; А.Б.С., Н.А.З., Ю.В.У. — методология, валидация, исследование, создание черновика; Е.М.Н. — редактирование рукописи, общее руководство.

Источник финансирования. Исследование выполнено при финансовой поддержке государственного задания «Поиск натуральных и синтетических вторичных метаболитов растений, обладающих противоопухолевыми и иммунокорригирующими свойствами на моделях *in vitro* и *in vivo*», номер регистрации 124022100044-2 от 2024 г.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов по представленной статье.

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DOI: https://doi.org/10.17816/KMJ634368