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Chelidonic Acid and its Derivates: General Spectrum of Biological Activity and Osteogenic Properties (Review)

Larisa A. Miroshnichenko, Tatiana Yu. Polyakova, Elena Yu. Avdeeva, Sergei V. Krivoshchekov✉, Igor A. Khlusov, Mikhail V. Belousov

Siberian State Medical University, 2, Moskovsky tract, Tomsk, 634050, Russia

✉ **Corresponding author:** Sergey V. Krivoshchekov. **E-mail:** ksv_tsu@mail.ru

ORCID: Larisa A. Miroshnichenko – https://orcid.org/0000-0002-3684-5510; Tatiana Yu. Polyakova – https://orcid.org/0000-0003-0971-7844; Elena Yu. Avdeeva – https://orcid.org/0000-0001-7061-9843; Sergei V. Krivoshchekov – https://orcid.org/0000-0001-5505-7141; Igor A. Khlusov – https://orcid.org/0000-0003-3465-8452; Mikhail V. Belousov – https://orcid.org/0000-0002-2153-7945.

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Abstract

Introduction. The development and implementation of new effective and safe drugs with osteogenic activity is an urgent problem of modern medical and pharmaceutical sciences. This is due to the wide prevalence and complexity of the treatment of diseases of the musculoskeletal system, which entails significant economic costs for the treatment and recovery of this group of patients. Recently, standard therapy regimens are increasingly being supplemented with drugs derived from medicinal plants, which is associated with their rather pronounced therapeutic effect and the absence or mild side effects compared to more expensive modern medical analogues. In this regard, the development of new directions in the strategy for the development of pharmacological agents from plant sources becomes relevant. The study of plant secondary metabolites is one such area that has already yielded good results in relation to the development of such drugs, and holds great promise. The review provides information on the biological properties of chelidonic acid and its possible derivatives in order to demonstrate the prospects for the use of these objects for the development of drugs, including those with osteogenic activity.

Text. Chelidonic acid is a substance present in many medicinal plants and has a wide range of pharmacological effects – analgesic, antimicrobial, anti-inflammatory, oncostatic and sedative. At the moment, methods have been developed for obtaining chelidonic acid and its derivatives from natural sources. In addition, chelidonic acid belongs to the so-called "small" molecules with osteogenic properties, which makes it promising in the creation of drugs for the treatment of diseases of the musculoskeletal system caused by impaired formation and regeneration of bone tissue. Native chelidonic acid has a low osteogenic activity, but given its ability to form complex compounds, it can act as a delivery system for osteoprotective micro- and macroelements. So, calcium chelidonate in experiments *in vitro* and *in vivo* shows a pronounced osteogenic activity: it stimulates the viability, adhesion and osteogenic differentiation of mesenchymal stem cells, enhances the mineralization of the extracellular matrix.

Conclusion. Taking into account the wide range of biological activity of chelidonic acid, its use in the complex therapy of allergies, depression, diabetes mellitus, inflammatory diseases, malignant neoplasms and other pathological conditions seems relevant. Calcium chelidonate is a promising drug candidate that can be used to accelerate regeneration processes and in bone tissue engineering.

Keywords: chelidonic acid, calcium chelidonate, γ-pyrones, osteogenic activity, osteoprotectors

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Хелидоновая кислота и ее дериваты: общий спектр биологической активности и остеогенные свойства (обзор)

Л. А. Мирошниченко, Т. Ю. Полякова, Е. Ю. Авдеева, С. В. Кривощеков✉, И. А. Хлусов, М. В. Белоусов

ФГБОУ ВО «Сибирский государственный медицинский университет», 634050, Россия, г. Томск, Московский тракт, д. 2

✉ **Контактное лицо:** Кривощеков Сергей Владимирович. **E-mail:** ksv_tsu@mail.ru

ORCID: Л. А. Мирошниченко – https://orcid.org/0000-0002-3684-5510; Т. Ю. Полякова – https://orcid.org/0000-0003-0971-7844; Е. Ю. Авдеева – https://orcid.org/0000-0001-7061-9843; С. В. Кривощеков – https://orcid.org/0000-0001-5505-7141; И. А. Хлусов – https://orcid.org/0000-0003-3465-8452; М. В. Белоусов – https://orcid.org/0000-0002-2153-7945.

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Резюме

Введение. Разработка и внедрение новых эффективных и безопасных лекарственных средств с остеогенной активностью является актуальной проблемой современной медицинской и фармацевтической наук. Это обусловлено широкой распространенностью и сложностью терапии заболеваний опорно-двигательного аппарата, что влечет за собой значительные экономические затраты на лечение и восстановление данной группы пациентов. В последнее время стандартные схемы терапии все больше дополняются препаратами, полученными из лекарственных растений, что связано с их достаточно выраженным терапевтическим воздействием и отсутствием или слабой выраженностью побочных эффектов по сравнению с более дорогими современными медицинскими аналогами. В связи с этим актуальным становится развитие новых направлений в стратегии разработки фармакологических средств из растительных источников. Изучение вторичных метаболитов растений является одной из таких областей, которая уже дала хорошие результаты в отношении разработки лекарств, и имеет большие перспективы. В обзоре представлена информация о биологических свойствах хелидоновой кислоты и возможных ее дериватов, с целью продемонстрировать перспективы применения этих объектов для разработки лекарственных средств, в том числе, с остеогенной активностью.

Текст. Хелидоновая кислота является веществом, присутствующим во многих лекарственных растениях, и обладающая широким спектром фармакологических эффектов – обезболивающий, противомикробный, противовоспалительный, онкостатический и седативный. На данный момент разработаны способы получения хелидоновой кислоты и ее дериватов из природных источников. Кроме того, хелидоновая кислота относится к так называемым «малым» молекулам с остеогенными свойствами, что делает ее перспективной в создании препаратов для лечения заболеваний опорно-двигательного аппарата, вызванных нарушением формирования и регенерации костной ткани. Нативная хелидоновая кислота обладает невысокой остеогенной активностью, но учитывая ее способность образовывать комплексные соединения, она может выступать системой доставки остеопротекторных микро- и макроэлементов. Так, хелидонат кальция в экспериментах *in vitro* и *in vivo* проявляет выраженную остеогенную активность: стимулирует жизнеспособность, адгезию и остеогенную дифференцировку мезенхимальных стволовых клеток, усиливает минерализацию внеклеточного матрикса.

Заключение. Принимая во внимание широкий спектр биологической активности хелидоновой кислоты, представляется актуальным ее использование в комплексной терапии аллергий, депрессий, сахарного диабета, воспалительных заболеваний, злокачественных новообразований и других патологических состояний. Хелидонат кальция является перспективным лекарственным кандидатом, который можно будет применять для ускорения процессов регенерации и в инженерии костной ткани.

Ключевые слова: хелидоновая кислота, хелидонат кальция, производные γ-пирона, остеогенная активность, остеопротекторы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Л. А. Мирошниченко, Т. Ю. Полякова проработали литературные источники, участвовали в написании текста статьи. Е. Ю. Авдеева проработала графический материал, участвовала в написании текста статьи. С. В. Кривощеков проработал литературные источники, участвовал в написании и утверждении текста статьи. И. А. Хлусов, М. В. Белоусов участвовали в написании и утверждении текста статьи.

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INTRODUCTION

Aspects of bone tissue regeneration in the context of an aging population, an increase in injuries and musculoskeletal (MS) diseases are a global fundamental and applied scientific problem of modern regenerative medicine. MS diseases are currently distinguished not only by their wide prevalence, diversity, but also by the complexity of treatment. Such diseases have a high social significance, as they reduce the quality of life and often lead to disability and death. In the structure of MS diseases, a significant percentage is taken by disorders related to the impairment of the formation and regeneration of bone tissue, which means there is a need to stimulate the process of osteogenesis. Complications of surgical treatment of bone fractures (osteomyelitis, non-united fractures, false joints) using implants and endoprostheses also require pharmacological correction with osteogenic agents. The administration of drugs that stimulate osteogenesis is extremely important in reconstructive surgery in the complementation of volumetric defects in tumor lesions of bone tissue. Recently, due to the growth of injuries and the widespread use of metalloosteosynthesis methods in the treatment of fractures, there has been an increase in the number of patients with chronic osteomyelitis [1, 2]. Despite the successes achieved in the treatment of osteomyelitis, the relapse rate reaches 40%, which is associated with

the need for repeated operations. The consequences of the disease are accompanied by significant economic costs for the treatment and pension provision of patients. Thus, MS diseases are not only a major medical, but also a socially significant problem.

In clinical medicine, bisphosphonates, denosumab, calcitonin, morphogenetic bone proteins (BMP) [3] and some other growth factors are used to control bone remodeling processes in various disorders, which often neutralize the benefits of specific osteogenic activity [4].

Recently, standard treatment regimens are increasingly supplemented with drugs derived from medicinal plants. The growing interest in products of natural origin is due to their rather pronounced therapeutic effect and the absence or weak severity of adverse effects compared to more expensive modern medical analogues. In this regard, the development of new directions in the strategy for the development of pharmacological agents from plant sources becomes relevant. The study of secondary plant metabolites is one such area that has already shown good results in relation to the development of such drugs and has great prospects. Modern research on new molecules with osteogenic activity is also developing in the field of natural compounds [5].

Of particular interest in the development of osteogenic agents are the so-called "small" molecules with osteogenic properties, which include helidonic acid (HA) contained in a number of medicinal plants, which has various types of biological activity, including osteogenic [6–9].

The ability of HA to chelate vital metal ions through coordination bonds [10] expands the spectrum of its pharmacological activity.

The review summarizes the literature on the biological activity of helidonic acid, one of the most important natural compounds of γ-pyrone, in order to assess the specific activity and possibility of use as drugs to stimulate bone regeneration.

SOURCES OF HELIDONIC ACID AND ITS DERIVATIVES

For the first time, helidonic acid (HA) also known as 2,6-dicarboxy-4-pyrone, 4-oxo-1,4-pyran-2,6-dicarboxylic acid, 4-oxo-4*H*-pyran-2,6-dicarboxylic acid, Jerva acid, jervaic acid and jervasic acid [11] isolated in 1839 from the milky juice of the stem of *Chelidonium majus* L. [12, 13], hence it received its name. HA is a heterocyclic organic acid found in more than 688 species of plants, such as: the fruits of the Moroccan palm, the flowers of the May lily, the sprouts of sorghum bicolor, etc. [14–17]. Helidonic acid is also found in alkaloid producer plants, where it forms ionic associates with the latter [18]. At the same time, as a secondary metabolite, helidonic acid may modulate the pharmacological activity of plant alkaloids [16].

The first works carried out in the 1960s and 1970s were devoted to the investigation of the processes underlying the synthesis of this natural compound by some plant species. It has been shown that HA is not a product of aromatic metabolism (Figure 1). Based on the results obtained in the study of the incorporation of radioactive molecules of glucose and ribose into the HA molecule, acid biosynthesis can go along the

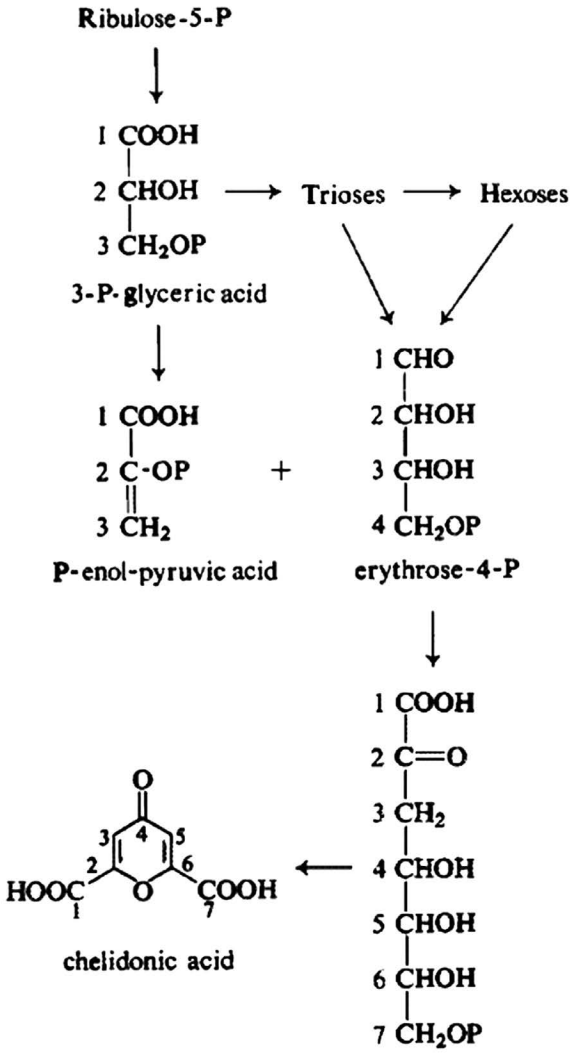

Figure 1. Scheme of the biosynthesis of chelidonic acid by Malcolm [20]

carbohydrate pathway. Based on the research data, three-carbon and four-carbon units formed as a result of the photosynthetic reduction cycle were offered as building blocks of the γ-pyrone [19, 20].

Later, studies appeared concerning the role of HA and its derivatives in provision of vital processes of plant organisms. So, it was found that potassium helidonate is responsible for nyctinasts (circadian movements of leaves) in some plants. In particular, it has been found to regulate the closure of the leaves of *Cassia mimosoides* at nightfall [21].

But even in the works of the beginning of the XXI century, the full pathway of HA metabolism remains completely unclear. The elucidation of the biosynthesis of helidonic acid is significantly difficult due to the inherent symmetry of the molecule [22, 23]. However, a number of investigators using a retrobiosynthetic approach on *Leucojum aestivum* cell suspension cultures have established that the carbon skeleton of helidonic acid is assembled from a single molecule of pentose and phosphoenolpyruvate [22].

The synthesis of HA is also possible in plants – hyperaccumulators of metals that accumulate organic acids and amino acids (as ligands) in response to the increasing intake of metals. Thus, in the studies by Chrisanne Naicker, it has been shown that *Berkheya coddii*, when exposed to a solution with a high concentration of nickel, enhances the synthesis of HA by more than 3 times compared to control. This may be the plant's response to the stress reaction associated with an increase in the nickel content which leads to the activation of HA synthesis to bind excess Ni. Based on these results, it can be concluded that HA is actually the ligand responsible for complexation with Ni in *Berkheya coddii* [23].

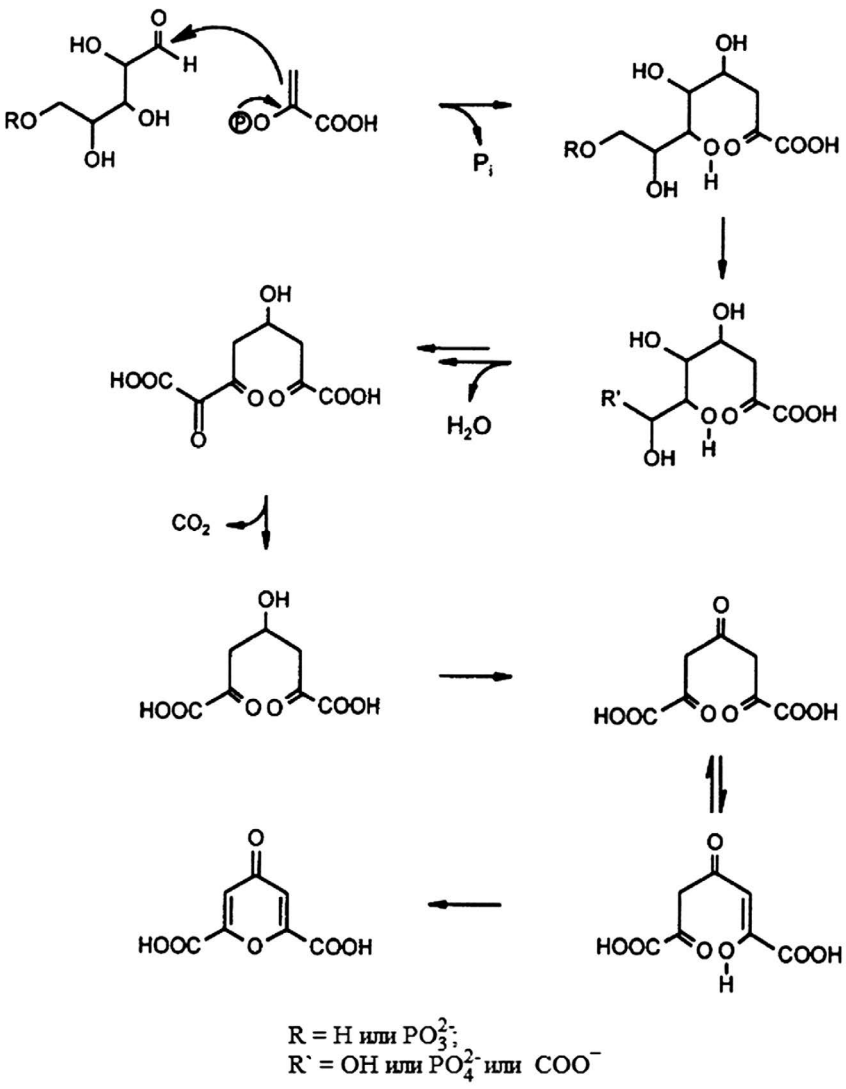

Figure 2. **Scheme of the biosynthesis of chelidonic acid by Ueda [22]**

This property of HA, namely the ability to chelate metal ions due to coordination bonds [10], has made it possible over the past few decades to synthesize and register various complexes of helidonic acid and the following metals – barium, zinc, copper, rare earth elements, nickel, etc. [10, 24–28]. These metal complexes are structurally characterized, and biological activity of some of them has also been investigated [30–41]. For example, the organometallic compound ruthenium(II) containing a chelidonate ligand was found to be more toxic against certain microorganisms than its parent ligand, while having antioxidant properties [40, 42].

There is also information on the molecular and supramolecular structures of five metalcomplexes synthesized from 4-oxo-4*H*-piran-2,6-dicarboxylic acid, namely tetraaquaberylium 4-oxo-4*H*-piran-2,6-dicarboxylate (I), hydrazine(2+) diaqua(4-oxo-4*H*-pyran-2,6-dicarboxylato)calcite (II), tetraaqua(4-oxo-4*H*-pyran-2,6-dicarboxylate)manganese(II) dihydrate (III), tetraaqua(4-oxo-4*H*-pyran-2,6-dicarboxylato) copper (II) (IV) and diaqua(4-oxo-4*H*-pyran-2,6-dicarboxylate) cadmium monohydrate (V). Complexes (I), (III) and (V) were obtained by direct interaction in an aqueous solution of 4-oxo-4*H*-piran-2,6-dicarboxylic acid with beryllium sulfate tetrahydrate, manganese (II) acetate and cadmium nitrate, respectively. Complex (IV) is synthesized in a similar manner using the basic copper carbonate. The anionic complex (II) was also obtained by this reaction, but in once distilled water, where the calcium component is assumed to remain. The data obtained also indicate an excellent coordination versatility of HA as a ligand and, as a result, the ability to participate in the formation of various structural complexes [10].

Several new metal complexes of helidonic acid ($helN_2$), namely

$$[Ca(hel)(H_2O)_3], [Cu(hel)(H_2O)_5] \cdot 2H_2O$$

$$и\ [VO\ (hel)(H_2O)_3] \cdot 2H_2O,$$

were obtained and identified by elemental analysis, characterized by electrochemical methods and IR spectroscopy, and their thermal stability was investigated by the TGA/DTA method. The mechanism of electrochemical reduction of HA on a static drop mercury electrode (SDM electrode) was investigated by cyclic rectangular voltammetry at different pH values. Its reduction on the SDM electrode is a kinetically controlled electrode reaction occurring with the transfer of one electron and two protons at $1 < pH < 6$, whereas in highly alkaline environments electron transport is independent of pH [42].

An improved synthesis of biologically active diethyl-4-oxo-4*H*-pyran-2,5-dicarboxylate (diethylisochelidonate) has also been developed, which involves the condensation of ethyl-2-(dimethylamino)methylene-3-oxobutanoate with diethyloxalate in the presence of sodium hydride. This method has several advantages, the main of which are simplicity, efficiency and availability of raw materials. Isochelidonic acid and its derivatives were obtained from diethylisohelidonate for the first time with a good yield. Taking into account this fact, namely the ability to convert an ester group into other functional groups, it has been once again confirmed that the nucleus of 4-pyrone-2,5-dicarboxylate is a universal "building block" for creating a wide range of 4-pyron derivatives [9].

At the same time, the growing interest in HA is due not only to its use in industry as a ligand in organometallic compounds for their separation, but also to the ability of HA to exert a wide range of pharmacological effects, namely analgesic, antimicrobial, anti-inflammatory, oncostatic and sedative actions [9, 17, 48–51].

TOTAL SPECTRUM OF BIOLOGICAL ACTIVITY

Antidepressant properties of helidonic acid

The investigation of antidepressant properties of HA in the "forced swimming" and "open field" test showed that oral administration of the acid to mice once a day for 14 days led to a significant decrease in immobility time in the forced swimming test without changing motor activity in the "open field" test. In addition, there was an increase in the number of Nissl bodies in the hippocampus, the expression of brain neurotrophic factor and estrogen receptor mRNAβ in the activation of phosphorylation of the protein kinase ERK [52].

Anti-inflammatory and immunomodulatory properties of helidonic acid

The anti-inflammatory properties of HA were characterized by a decrease in the level of hippocampal IL1β, IL6 and TNF-α in a significant increase in serotonin,

dopamine and norepinephrine levels compared with those in mice that were administered with distilled water [52].

The anti-inflammatory properties of HA were also shown in a model of ulcerative colitis induced by sodium dextran sulfate. The administration of the acid diminished clinical signs of intestinal inflammation (loss of body weight and shortening of the length of the colon). In addition, HA has been found to regulate serum levels of IL6 and TNF-α, and in the tissues of the colon, the production of prostaglandin E_2 (PGE2) and the expression levels of cyclooxygenase-2 (COX-2) and hypoxia-induced factor-1α (HIF-1α), leveling their increase [51]. A significant reduction in TNF-α levels was also observed in an inflammation model of oral keratinocytes cultured for 24 hours with 5 % cigarette smoke extract and treated with Kouyanqing Granule, which include HA as one of the biologically active ingredients [53]. Recurrent aphthous ulcers, oral mucositis, lichen planus, and other inflammatory oral disorders are usually associated with the secretion of various pro-inflammatory cytokines (e.g., TNFα, IL1β, IL6, IL8, etc.) [54–57]. Thus, modulation of the production of these HA cytokines can contribute to the restoration of the mucous membrane in inflammatory oral diseases of the oral cavity.

Hyun-Ji Shin et al. investigated the effect of HA on the mechanisms of regulation of the inflammatory response mediated by mast cells of the HMC1 line using forbolic ester $C_{36}H_{56}O_8$ (forbol-12-myristate-13-acetate) and calcium ionophore A23187 [50]. The acid has been shown to inhibit IL-6 production and IL-6 mRNA expression by blocking the nuclear factor NF-kB. Helidonic acid also reduced inflammatory responses by suppressing activation and expression of caspase-1, which is also confirmed by the data obtained by Hyun-A Oh and colleagues, on a model of allergic rhinitis in mice sensitized with ovalbumin. Oral administration of HA significantly reduced the number of nose/ear rubs in mice with allergic rhinitis by reducing histamine, IgE levels, and reducing infiltration by eosinophils and mast cells. A decrease in the level of IL-4 was accompanied by a significant increase in the level of IFNγ, which suggests the influence of HA on the cellular component of the immune response [58].

The immunomodulatory effects of HA have been confirmed in studies in rats immunized with ovalbumin. HC was administered intraperitoneally to animals in doses of 1, 3 and 10 mg/kg. *Ex vivo* and *in vitro* experiments have shown that HA inhibits mast cell degranulation caused by ovalbumin and histamine release regardless of the immunological or other mechanisms involved in such release. In addition, there was a dose-dependent decrease in the number of eosinophils and the level of IgE in the blood after administration of HA [59]. In this regard, it can be assumed that the immunomodulatory reactions of HA to allergic agents (ovalbumin) depended on the level of IgE and were mediated by Th2 cells. It should be noted that these effects of the study drug were comparable to the effects of prednisone. At the same time, the use of HA reduced by 40 % the death of animals from anaphylactic shock caused by the administration of prednisone. In addition, 14-day administration of HA at a dose of up to 20 mg/kg did not cause signs of acute toxicity.

In classical tests for the evaluation of humoral and cell-mediated immunity, it is shown that the test substance inhibits the antibody-mediated response to the administration of red blood cells of the sheep in mice and also reduces the number of cells that form splenic plaques. In addition, the specific level of IgG also decreased with the administration of HA compared with the control (without HA treatment). At the same time, in tests for delayed hypersensitivity (HRT), HA caused a decrease in reaction. HRT compared to the control group, which presumably indicates the suppression of cell-mediated immunity by the study drug. However, these effects were independent of HA dose and may be related to the non-specific nature of the immune response [59]. These results suggest that HA has an immunosuppressive effect in adaptive immunity tests, which may emphasize its modulating effect in other immune-mediated disorders.

The data obtained confirm the significant immunomodulatory and anti-inflammatory properties of helidonic acid in experimental allergy models and suggest the possibility of using this molecule of plant origin in the treatment of allergic and anti-inflammatory diseases.

Inhibitory effect of helidonic acid

Studies by T. G. Porter and D. L. Martin have shown that HA is a potent inhibitor of glutamate dehydrogenase. Kinetic analysis of HA inhibition revealed that this compound was competitive with glutamate with a Ki value of 1.2 μM, it inhibited glutamate-dependent apoenzyme formation by blocking the penetration of glutamate into the active site of the enzyme, but did not affect the absorption of free pyridoxal phosphate. Thus, HA can be considered as a potential agent involved in the regulation of the synthesis of gamma-aminobutyric acid [60].

HA is also an inhibitor of dihydrodipicolinate synthase, a key enzyme in the biosynthesis of lysine via the aminopimelate pathway [61].

There is evidence of the possibility of using HA derivatives as an inhibitor of BACE1 (b-secretase, a protein precursor of amyloid). A group of authors synthesized non-peptide and small-sized inhibitors of BACE1 having a helidonic or 2.6-pyridindicarbon heterocyclic carcass at position P2, which are comparable in permeability across the blood-brain barrier to potent pentapeptide inhibitors of BACE1, but have much better bioavailability due to high enzymatic stability [62].

Antitumor effects of helidonic acid

The study of anticarcinogenic properties of organotin HA polyesters is due to the available data on the antitumor effects of organotin compounds [63–65], as well as on the high biological activity of HA. Organotin polyesters of HA are obtained as a result of an interphase reaction between the disodium salt of helidonic acid and various organotin dihalides. The toxicity of each test compound was assessed on the human pancreatic adenocarcinoma cell line (AsPC1) and the human pancreatic epithelioid ductal carcinoma cell line (PANC1). It was shown that organotin HA polymers more significantly inhibit the growth of pancreatic cancer cells in comparison with monomeric organotin fragments. Similar results were obtained when compared with cisplatin. Perhaps this is due to both the polymeric nature of the materials and the ability of organotin compounds to inhibit the growth of cancer cells at once at several stages, while the cytostatic acts only through chelation of the DNA itself [11]. The data obtained will certainly allow advancing in the expansion of the range of anti-cancer agents.

Antidiabetic properties of helidonic acid

According to the literature, in rats with streptozotocin-induced diabetes, administration of the methanol extract of *T. cannabina* led to a decrease in blood glucose levels [66]. The information obtained suggested the presence of hypoglycemic action in the pyran ether (bis-(6-methylheptyl) ester of 4-oxo-4*H*-piran-2,6-dicarboxylic acid), isolated from the chloroform extract of the root of *T. cannabina*, by column chromatography. In a model of fertilized eggs of white leghorn chickens treated with streptozotocin, it was shown that the administration of this compound in doses of 0.5 mg/egg and 1 mg/egg had a dose-dependent antihyperglycemic effect. Pyran ether in the docking analysis showed a good binding ability to the active site of AMP kinase, comparable to metformin. The results obtained in studies *in silico* demonstrated dose-dependent efficacy and correlation with *in vitro* experiments. However, for a full assessment of the antidiabetic effects of this substance, additional *in vivo* studies are needed, as well as, a comprehensive study of biological safety and clinical efficacy [67].

Pronounced analgesic activity of γ-pyron derivatives, including HA, has been experimentally shown [68–71].

In particular, HA is of interest as a ligand of organometallic compounds in plants [10, 29], and a possible way to deliver vital elements to target organs.

Osteogenic activity of helidonic acid in vivo and in vitro

In a series of experiments, data were obtained for the first time on the osteogenic activity of HA isolated from *Saussurea controversa* both in the native state and in combination with calcium [$Ca(Cha)(H_2O)_3$], as well as synthesized *n*-monobutyl ester of chelidonic acid and calcium helidonate obtained semi-synthetically using natural HA [72, 73].

According to the results of *in vitro* stromal cell testing, HA and *n*-monobutyl ester of HA showed low activity relative to osteogenic differentiation of a culture of multipotent mesenchymal stromal cells from

human adipose tissue (hMMSC-AT). At the same time, high doses of these substances showed cytotoxicity and reduced the number of cells in culture, depending on the balance of the processes of cell proliferation, differentiation and apoptosis. In their turn, the tested doses of natural calcium chelidonate significantly stimulated the level of cell viability, enhanced the differentiation of hMMS-AT into osteoblasts and mineralization of the culture of hMMS-AT compared with both control and comparators. There is evidence that the calcium helidonate fraction of *S. controversa* extract showed osteogenic activity *in vivo* in experimental osteomyelitis in rats (table 1) [74, 75].

X-ray diffraction analysis demonstrated the identity of the structure of the semi-synthetic calcium helidonate and the sample isolated from natural raw materials [72]. The osteogenic activity of semi-synthetic calcium chelidonate was studied *in vitro* on a 21-day culture of hMMS-AT and *in vivo* in mice using ectopic (subcutaneous) implantation of titanium plates coated with CaP saturated *in vitro* with syngenous bone marrow. When using an aqueous solution of calcium helidonate at a dose of 10 mg/kg, there was an increase in the mineralization of the extracellular matrix *in vitro* and the formation of ectopic bone tissue *in situ*. The test substance contributed to the differentiation of multipotent mesenchymal stromal/stem cells of human adipose tissue, as well as mouse mesenchymal stem cells into osteoblasts *in vitro* and *in vivo*, respectively (table 1) [73].

The results obtained allowed the authors to propose potential targets for calcium helidonate. These can be bone morphogenetic protein 2 (BMP-2), transcription factor 2 (RUNX2) and Wnt pathway [76], as well as small osteogenic molecules such as β-glycerophosphate, dexamethasone and ascorbic acid; adenosine [via the phosphatadenosine triphosphate (ATP) axis – adenosine receptor A2b (A2bR)] and a derivative of helioxanthin 4-(4-metoxyphenyl)-pyrido[40,30:4,5]thieno-[2,3-b] pyridine-2-carboxamide [77] or calcium (via Ca^{2+} sensitive receptor). Given all of the above, as well as the non-toxicity of the calcium salt of HA, the authors believe that calcium helidonate is a promising substance for accelerating the processes of bone tissue regeneration and engineering.

Thus, despite the low osteogenic activity of native HA, but given its ability to form chelated compounds,

Table 1. Osteogenic activity of chelidonic acid and its derivatives in vivo and in vitro

Substance	Production method	Osteogenic activity		References
		in vitro	*in vivo*	
Chelidonic acid	Natural source	Weak activator of osteogenic differentiation of hAMMSC culture. Cytotoxin in high doses		[72]
Calcium chelidonate	Natural source	Stimulation of cell viability, enhancement of hAMMSC differentiation into osteoblasts and mineralization of hAMMSC culture	Osteogenic activity in experimental osteomyelitis in rats	[72, 74, 75]
n-monobutyl ester of chelidonic acid	Semi-synthetic	Weak activator of osteogenic differentiation of hAMMSC culture. Cytotoxin in high doses		[72]
Calcium chelidonate	Semi-synthetic	Increased mineralization of the extracellular matrix and osteogenic differentiation of hAMMSC	Enhancement of viability, adhesion and osteogenic differentiation of MSCs on the surface of CaP-coated implants under biomechanical cyclic loads caused by movement of muscles and skin in mice.	[73]

it can act as a delivery system for osteoprotective trace elements, such as calcium, magnesium, strontium, which have a significant impact on the processes of bone tissue regeneration and on the normal bone structure [78–81].

It should be noted that the search for systems for the delivery and targeting of therapeutic agents to bone tissue is an important problem [82–84]. It is known that organic molecules with chelating properties, including HA can be a method to deliver mineral components to tissues and lead to an increase in the selectivity of their therapeutic effect on bone tissue [85].

CONCLUSION

Summarizing the literature data, it can be concluded that further explorative and preclinical pharmacological studies of the specific activity of helidonic acid and its compounds, the search for targets of their pharmacological effects, as well as the possibility of using helidonic acid in the complex therapy of musculoskeletal diseases, motor apparatus, allergies, depression, diabetes, inflammatory diseases, malignant neoplasms and other pathological conditions is very promising. At the same time, not only investigation of natural complex compounds of helidonic acid is of considerable interest, but also the possibility of synthesizing candidate substances based on the acid as promising osteoprotectors.

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