Review article
УДК 577.1
DOI: 10.31857/S0869769824030011
EDN: ISWKGZ

# Marine Natural Products: The Long Road to Drug Discovery*

H.K. Kim, M.V.F.V. Garcia, N. Shepetova*, J. Han

*Hyoung Kyu Kim*
PhD, Professor
Cardiovascular and Metabolic Disease Center, Smart Marine Therapeutic Center,
College of Medicine, Inje University, Busan 614-735, Korea;
Professor
Department of Health Sciences and Technology, Graduate School of Inje University,
Busan 614-735, Korea;
Professor
Department of Physiology, College of Medicine, Inje University, Busan 614-735, Korea
estrus74@gmail.com

*Maria Victoria Faith V. Garcia*
PhD, Post-doctoral Researcher
Cardiovascular and Metabolic Disease Center, Smart Marine Therapeutic Center,
College of Medicine, Inje University, Busan 614-735, Korea;
Post-doctoral Researcher
Department of Health Sciences and Technology, Graduate School of Inje University,
Busan 614-735, Korea
victoriafaith.garcia@gmail.com

*Natalia Shepetova*
Assistant Director for International Relations
G.B. Elyakov Pacific Institute of Bioorganic Chemistry,
Far East Branch of the Russian Academy of Sciences, Vladivostok, 690022, Russian Federation
piboc@bk.ru

*Jin Han*
MD, PhD, Professor, Director
Cardiovascular and Metabolic Disease Center, Smart Marine Therapeutic Center,
College of Medicine, Inje University, Busan 614-735, Korea;
Professor
Department of Health Sciences and Technology, Graduate School of Inje University,
Busan 614-735, Korea;
Professor
Department of Physiology, College of Medicine, Inje University, Busan 614-735, Korea
phyhanj@inje.ac.kr, phyhanj@gmail.com
*These authors contributed equally to this work.
✉Authors to whom correspondence should be addressed.


* Публикуется в авторской редакции.

***Abstract.*** The collaboration between various research institutions in South Korea and G.B. Elyakov Pacific Institute of Bioorganic Chemistry (PIBOC) in Russia started 30 years ago in 1993. Since then, we have been actively conducting marine biotechnology and pharmaceutical research. For nearly 20 years, this successful partnership has been led by the exceptional "conductor" Valentin Stonik, who has formed an exquisite harmony "orchestra" that we have named KORUS MUSIC (Korea-Russia collaboration for Marine Unlimitedre Sources for Innovation and Creation). The purpose of this review paper is to present the history of KORUS MUSIC and highlight the significant advances achieved through our joint research, and to outline plans for our future collaboration and joint efforts for the next 20 years. This article is a synthesis of science and poetry, of the history of friendly relations and dreams of a common future. It is dedicated to the 80th anniversary of Prof. Stonik, to the 60th anniversary of PIBOC and to the 30th anniversary of collaboration between the Korean and Russian scientists.

***Keywords:*** marine natural products, frondoside, cucumarioside, stichoposide, echinochrome, spinochrome, neopetroside

***For citation:*** Kim H.K., Garcia M.V.F.V., Shepetova N., Han J. Marine Natural Products: The Long Road to Drug Discovery. *Vestnik of the FEB RAS.* 2024;(3):12–36. (In Engl.). http://dx.doi.org/10.31857/S0869769824030011

Обзорная статья

# Морские природные продукты: долгий путь к открытию лекарств

Х.К. Ким, М.В.Ф.В. Гарсия, Н.М. Шепетова✉, Д. Хан

*Хен Кю Ким*
доктор философии, профессор
Центр сердечно-сосудистых и метаболических заболеваний, Центр морской терапии, Медицинский колледж, Университет Индже, Пусан, 614-735, Корея;
профессор
Факультет медицинских наук и технологий, Высшая школа Университета Индже, Пусан 614-735, Корея;
профессор
Кафедра физиологии, Медицинский колледж, Университет Индже, Пусан 614-735, Корея
estrus74@gmail.com

*Мария Виктория Фейт В. Гарсия*
доктор философии, докторант-исследователь
Центр сердечно-сосудистых и метаболических заболеваний, Центр морской терапии, Медицинский колледж, Университет Индже, Пусан, 614-735, Корея;
докторант, научный сотрудник
Факультет медицинских наук и технологий, Высшая школа Университета Индже, Пусан 614-735, Корея
victoriafaith.garcia@gmail.com

*Наталья Михайловна Шепетова*
помощник директора по международным связям
Тихоокеанский институт биоорганической химии имени Г.Б. Елякова ДВО РАН, Владивосток, Россия
piboc@bk.ru

*Джин Хан*
доктор медицины, доктор философии, профессор, директор
Центр сердечно-сосудистых и метаболических заболеваний, Центр морской терапии, Медицинский колледж, Университет Индже, Пусан, 614-735, Корея

профессор
Факультет медицинских наук и технологий, Высшая школа Университета Индже, Пусан, 614-735, Корея
профессор
Кафедра физиологии, Медицинский колледж, Университет Индже, Пусан 614-735, Корея
phyhanj@inje.ac.kr, phyhanj@gmail.com
*Все авторы внесли равный вклад в эту работу.
✉Авторы, которым следует направлять корреспонденцию.

***Аннотация.*** Сотрудничество между научно-исследовательскими институтами Южной Кореи и Тихоокеанским институтом биоорганической химии имени Г.Б. Елякова (ТИБОХ) в России началось 30 лет назад, в 1993 году. С тех пор мы активно ведем исследования в области морской биотехнологии и фармацевтики. На протяжении почти 20 лет это успешное партнерство возглавлял выдающийся "дирижер" профессор Валентин Стоник, сформировавший изысканный гармоничный "оркестр", который мы назвали KORUS MUSIC (Korea-Russia collaboration for Marine Unlimitedre Sources for Innovation and Creation). Цель данной обзорной статьи – рассказать об истории создания KORUS MUSIC и отметить значительные успехи, достигнутые в ходе наших совместных исследований, а также наметить планы нашего дальнейшего сотрудничества и совместных усилий на ближайшие 20 лет.

***Ключевые слова:*** морские природные продукты, фрондозид, кукумариозид, стихопозид, эхинохром, спинохром, неопетрозид

***Для цитирования:*** Kim H.K., Garcia M.V.F.V., Shepetova N., Han J. // Marine Natural Products: The Long Road to Drug Discovery // Вестн. ДВО РАН.2024. № 3. С. 12–36. (In Engl.). http://dx.doi.org/10.31857/S0869769824030011

## 1. Introduction

Research on marine natural products began in the 1960s. These compounds found in marine organisms have a wide structural diversity, suggesting that they are produced by unusual biochemical pathways. Marine natural products are of interest as modulators of chemical-ecological interactions and as potential ingredients in pharmaceuticals and other products, such as food supplements and markers for taxonomy.

The G.B. Elyakov Pacific Institute of Bioorganic Chemistry (PIBOC) was founded in 1964 within the Russian Academy of Sciences (RAS). Currently there are 311 employees, including one Full Member of the RAS, one Corresponding Member of the RAS, 30 DSc and 79 PhD. In addition to basic research on biologically active compounds from marine organisms, the Institute's works also pursue practical goals such as the development of new products for medicine, biotechnology, microbiology and agriculture. For nearly 60 years, PIBOC scientists have achieved significant results in this way and established a rich network of scientific collaboration and warm relationships with other institutes worldwide, not only in the Republic of Korea, but also in China, France, Germany, Italy, Japan, Spain, Vietnam and others.

The Republic of Korea, popularly known as South Korea, is one of the leading countries in Asia that conducts extensive marine drug research. This country has 2,413 km of coastline, making it a prime area for the search for natural marine organisms and the diverse study of their metabolites. Traditional Korean medicine has always used marine products to treat various diseases, and in the early 20th century began systematic medical research on these products. In the 1970s, the Korean government established research institutes dedicated to marine natural products. The partnership between PIBOC and the Korean institutes made sense due to our common academic interests in the development of new drugs and natural food supplements from these products. The first collaboration in 1993 began the beautiful symphony that we named the Korea-Russia Marine Unlimited reSources for Innovation and Creation (KORUS MUSIC). Together, we have now reached a "crescendo" in marine drug research and can do even more in the future.

The goal of the Korean-Russian (KORUS) collaboration is to develop innovative treatments using natural products from marine organisms on various disease models. This collaboration

is possible due to our synergistic approach and experience in this field. Our facilities, techniques and research paradigms are highly complementary. The Korean scientists and our Russian colleagues are fully aware of the unique opportunity to create new trends in marine natural product research for the development of both our countries.

## 2. Valentin A. Stonik: The Maestro of KORUS MUSIC

Professor, DSc Valentin Stonik (Figure 1) is one of the leading figures in natural products chemistry, chemistry of physiologically active compounds and their secondary metabolites from marine invertebrates. He was born in Vladivostok (Russia), graduated from the Chemistry Department of the Far-Eastern State University (Vladivostok) in 1965, received his Ph.D. in 1969, and his DSc in Bioorganic Chemistry in 1988. He started his research career at the Institute of Biologically Active Substances (it is now G.B. Elyakov Pacific Institute of Bioorganic Chemistry, Far-Eastern Branch of the Russian Academy of Sciences) as a junior researcher (1970), then became the Director of the Institute (2002–2017) and Scientific Supervisor (2017–present). For his great contribution to science, Prof. Stonik received the high academic titles of Corresponding Member of the Russian Academy of Sciences (1997) and then Full Member of the Russian Academy of Sciences (Academician, 2000).

Prof. Stonik's enthusiasm and special interests focus on structural studies, biological activities, biosynthesis, chemotaxonomy, and chemical evolution of marine natural products. He is a prolific author of about 500 scientific articles published in Russia and worldwide, as well as a textbook, 3 monographs, and 20 patents. Due to the depth and breadth of his knowledge, he is a valued member of the editorial boards of several scientific journals, such as Natural Product Communications, Natural Product Letters, Russian Journal of Bioorganic Chemistry, and Marine Drugs. In 2018, he became the Scientific Supervisor of PIBOC, and his leadership continues with publications and collaborations that within the KORUS partnership.

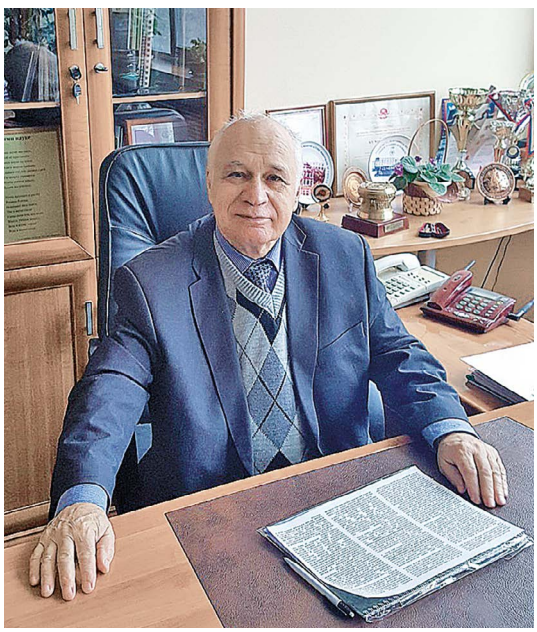

Fig. 1. Prof. Valentin Stonik, Scientific Supervisor of the G.B. Elyakov Pacific Institute of Bioorganic Chemistry, Far-Eastern Branch of the Russian Academy of Sciences

Prof. Stonik has been instrumental in establishing and maintaining the KORUS partnership. Important patents and publications have been generated under his leadership. Without his expertise, the depth and breadth of our scientific results would not be as significant. His enthusiasm for building relationships, openness to collaboration, and constant attention are contagious and drive our group to pursue new research goals.

## 3. History of KORUS collaboration

In 1993, PIBOC's first partnership began with one of our Korean research groups, the Tobacco and Ginseng Institute in Daejeon. At that time, PIBOC was headed by Professor Elyakov, who collaborated with Professor Hoon Pak on the study of ginseng glycosides and their related

synthetic analogs. The collaboration resulted in the synthesis of the natural metabolite Rg found in ginseng (1994–1995). The establishment of the Korea Ocean Research and Development Institute (KORDI) in Ansan opened the way for PIBOC to collaborate with Dr. San-Jin Kim, who participated in the marine expedition in the Sea of Okhotsk aboard the research vessel "Akademik Oparin". In turn, KORDI invited PIBOC to participate in its project on monitoring of environmental and seawater pollution (1996–1997). Joint meetings were held in Korea in 2005. The first Memorandum of Understanding between PIBOC and the Medical Center of Dong-A University (Busan) was signed in September 2005, and two years later, in August 2007, we all met again for the first Russian-Korean Scientific Symposium, which was held in Vladivostok (Russia).

The relationship between KORDI and PIBOC was formalized by a Russian-Korean Agreement in 2008, when KORDI was renamed to Korea Institute of Ocean Science and Technology (KIOST). This partnership successfully produced eight journal articles on "Bioactive natural products from Far-Eastern marine organisms: searching, isolation, structure elucidation, and biological activity" co-authored by Prof. Stonik and Dr. Makarieva from PIBOC and Dr. Hyi-Seung Lee from KIOST. In 2008, we met again in Russia at the 1st International Symposium on Life Sciences organized by PIBOC. The second Russian-Korean scientific symposium was held in Keo-Je, Korea, in 2009.

Since 2005, the Immune-network Pioneer Research Center, headed by Professor Jong-Young Kwak, has been successfully collaborating with PIBOC under the KORUS partnership. In 2016, a Memorandum of Understanding was signed with Ajou University where this Center is now affiliated. In 2012, Professor Kwak was awarded the honorary degree of "*Doctor Honoris Causa*" by the Russian Academy of Sciences for his significant contribution to the Russian-Korean scientific collaboration.

Inje University also joined the KORUS partnership in 2014, with a Memorandum of Understanding with PIBOC and Ajou University. This was made possible under the leadership of Dr. Stonik from PIBOC and Dr. Jin Han from the Cardiovascular and Metabolic Disease Center (CMDC) of Inje University. The excitement of our collaboration focused on the marine natural products and the novel therapeutic modalities for cardiovascular diseases. In June 2017, another Memorandum of Understanding was signed between PIBOC, Inje University, and this time with Inje Paik Hospital, which was a joint success inspired by Professors Han and Stonik. This partnership resulted in the Marine Therapeutic International Institute Project, which aimed to develop new marine drugs. In 2014, the KORUS Symposium was hosted by Inje University in Busan, and after a year's break, we all came together again for the KORUS-2016 Symposium in Vladivostok, and then again in Busan for KORUS-2017.

Under the KORUS partnership, the Laboratory of Microbiology of PIBOC has fruitfully collaborated for many years with the Korean Collection of Type Cultures, the Bio-Medical Research Institute of Kyungpook National University Hospital, Chungnam National University, and other institutions. In addition, the Laboratory of Enzyme Chemistry has conducted research on marine algae polysaccharides together with the Medical Center of Daegu Catholic University, the Korean Institute of Science and Technology in Gangneung, and the College of Pharmacy of Chosun University.

The KORUS partnership has fostered an enriching research environment, especially through our ability to come together for research projects such as the International Research Exchange Support Project selected by the Korea Research Foundation in 2014. In August 2017, we established the KORUS Science and Technology Joint Research Project, which was selected by the Ministry of Science and Technology of the Korean government. Also in 2017, we planned and implemented the Korea Marine Therak Future Project Group (BISTEP Support). In 2020, we prepared a survey report on technology development projects for the commercialization of foreign source technologies. We have successfully brought together a large network of research professionals from across Korea and promoted capacity building in our collaborative research efforts. These relationships have been further strengthened through several joint memoranda of understanding that have formalized our collaborations and partnerships, ensuring greater success through mutual support of each other's research efforts (Supplementary Lists 1–3).

The scientific relations and research are successful thanks to the leadership of Dr. Valentin Stonik. Through the KORUS Symposia held over the years, starting in 2007 and most recently in 2019, alternating between Vladivostok and Korea, many scientists had the opportunity to meet, make friends, and exchange ideas. Korean scientists also participated in the International Symposium on Life Sciences, which was held three times in Vladivostok (2008, 2013, and 2018). All this promoted both Russian and Korean research on marine natural products, resulting in patents, journal articles, new research projects, symposia, and conferences with our colleagues all over Korea (Figures 2, 3).

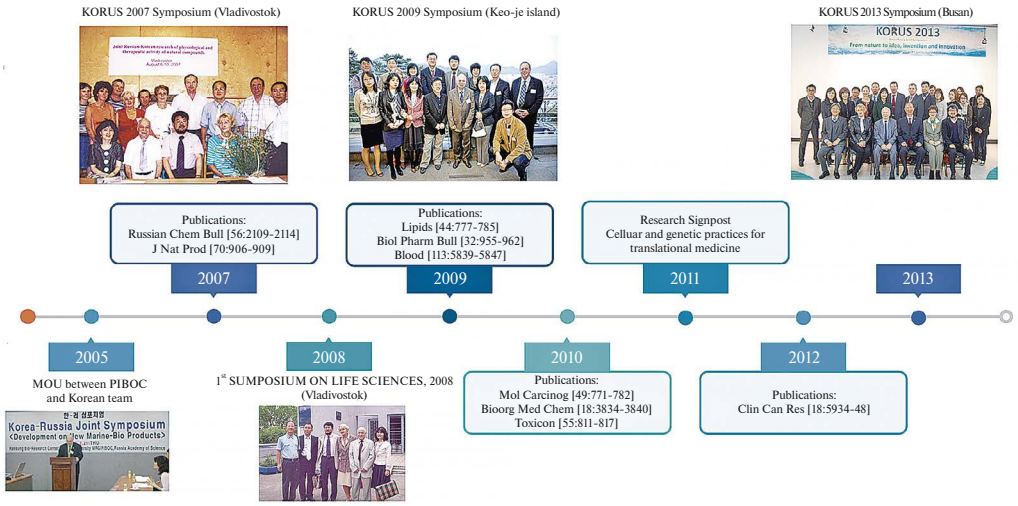


Fig. 2. Timeline of KORUS publications, patents, and symposia through the years of research and friendship, 2005–2013. Images rendered by Biorender.com. Image usage is covered by BioRender's Academic License Terms

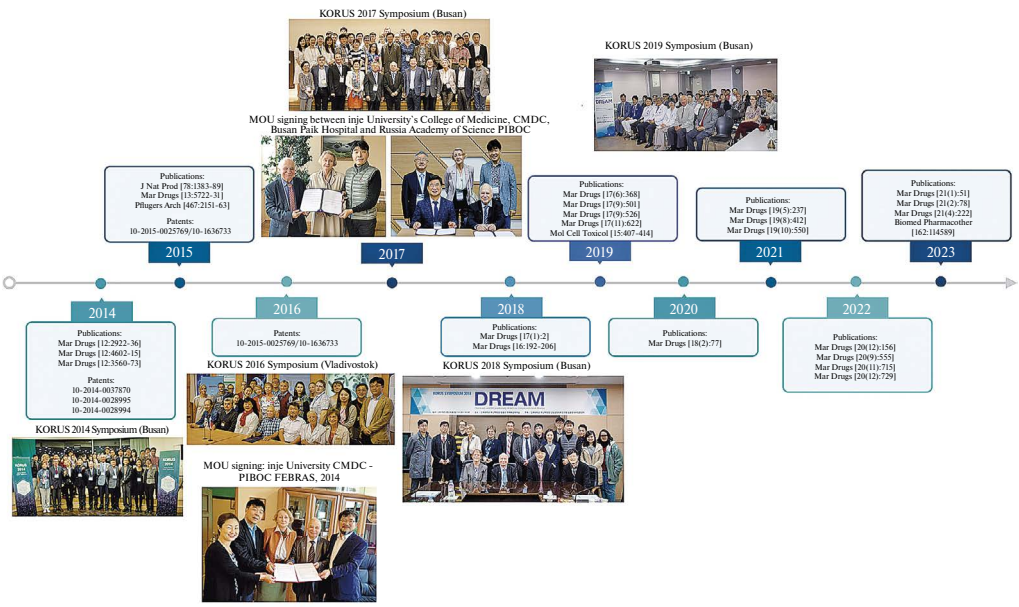


Fig. 3. Timeline of KORUS publications, patents, and symposia, 2014–2019. Images rendered by Biorender.com. Use of the images is subject to BioRender's Academic License Terms

## 4. Medical Advancements and Impact

Medicine has always tried to improve on traditional methods of treatment. The natural world, especially the Ocean, will always open new frontiers for scientific discovery. The Ocean is full of mysterious inhabitants that seem familiar but remain unknown or little studied. The diversity of marine flora and fauna makes it possible to search for unique and potent compounds with biological activity, which can be the basis for new medicines. Life in both our countries, Russia and the Republic of Korea, is connected with the sea, and we have many opportunities for marine research, especially for marine biotechnology. The potential benefits of marine biotechnology include:

- New drug resource: Marine organisms may contain compounds which help them to survive and adapt under special environmental conditions and which may be utilized for new drugs against various diseases [1].
- Novel drug target: The environment influences the survival and persistence of marine organisms in the oceans. Interactions between marine organisms and their environment can provide insights into the molecular basis of disease, and studies that detect changes in protein or genetic profiles can help for drug development [2].
- Potential mode of drug delivery: Marine organisms may also produce biopolymers with unique structures that can be used to deliver new drugs to specific tissues and cells, providing structural stability of drugs or reducing their side effects [3].
- Potential diagnostic tools: Marine organisms may have specific nucleic acids and proteins that can be used for assay development or disease detection based on their unique structural features [4].
- Prospective disease models: Numerous studies have used marine organisms to diagnose disease or explain physiological mechanisms. Studying the response of marine organisms to stress, injury, or disease can provide insight into novel disease mechanisms that can be used to develop strategies for prevention and treatment [5].

The collaboration between Korea and Russia has successfully resulted in publications and patents, in particular, we have 8 international patents (Table 1) and 93 journal articles (Table 2)

Table 1

**Korean-Russian patent applications and registered patents**

| | Patent Title | Application and Registration Number |
|---|---|---|
| 1 | Composition for inducing differentiation of cardiomyocytes comprising echinochrome A | 10-2016-0026942<br>PCT/KR2016/002267 |
| 2 | Pharmaceutical composition for preventing or treating ischemic heart disease containing neopetroside A as an active ingredient | 10-2016-0026943/<br>PCT/KR2017/005645<br>10-1788589 |
| 3 | Health food composition for enhancing exercise ability comprising echinochrome A and method for enhancing exercise ability using the same | 10-2015-0025769/<br>10-1636733 |
| 4 | Pharmaceutical composition for preventing or treating degenerative neurological disease comprising echinochrome | 10-2014-0037870 |
| 5 | Composition of controlling the function of mitochondria comprising echinochrome A | 10-2014-0028995 |
| 6 | Composition of preventing or treating for myocardial damage containing echinochrome A | 10-2014-0028994 |
| 7 | Pharmaceutical composition for preventing or treating myocardial damage comprising Spinochrome D | 10-2019-0141881 (Application)<br>10-2213913 (Registration) |
| 8 | Neopstrosides A and B and synthesis method thereof | US 10,927,101 B2 |

focused on marine natural products and their potential in various clinical applications. More recently, we have been able to focus on marine compounds from sea cucumbers, sea urchins, and sea sponges and their applications in various medical fields (Figure 4).

Table 2

**List of KORUS publications (2014–2023)**

| | Title | Year | Journal | Reference |
|---|---|---|---|---|
| 1 | Echinochrome A protects mitochondrial function in cardiomyocytes against cardiotoxic drugs | 2014 | Marine Drugs | [6] |
| 2 | Echinochrome a increases mitochondrial mass and function by modulating mitochondrial biogenesis regulatory genes | 2014 | Marine Drugs | [7] |
| 3 | Acetylcholinesterase inhibitory activity of pigment echinochrome A from sea urchin *Scaphechinus mirabilis* | 2014 | Marine Drugs | [8] |
| 4 | Echinochrome A regulates phosphorylation of phospholamban Ser16 and Thr17 suppressing cardiac SERCA2A $Ca^{2+}$ reuptake | 2015 | Pflugers Arch | [9] |
| 5 | Pyridine nucleosides neopetrosides A and B from a marine *Neopetrosia sp.* sponge synthesis of neopetroside A and its beta-riboside analogue | 2015 | J Nat Prod | [10] |
| 6 | Echinochrome A improves exercise capacity during short-term endurance training in rats | 2015 | Marine Drugs | [11] |
| 7 | Spinochrome D attenuates doxorubicin-induced cardiomyocyte death via improving glutathione metabolism and attenuating oxidative stress | 2018 | Marine Drugs | [12] |
| 8 | A novel atypical PKC-Iota inhibitor, echinochrome A, enhances cardiomyocyte differentiation from mouse embryonic stem cells | 2018 | Marine Drugs | [13] |
| 9 | The protective effects of echinochrome A structural analogs against oxidative stress and doxorubicin in AC16 cardiomyocytes | 2019 | Molecular & Cellular Toxicology | [14] |
| 10 | Therapeutic cell protective role of histochrome under oxidative stress in human cardiac progenitor cells | 2019 | Marine Drugs | [15] |
| 11 | Echinochrome A attenuates cerebral ischemic injury through regulation of cell survival after middle cerebral artery occlusion in rat | 2019 | Marine Drugs | [16] |
| 12 | Echinochrome A reduces colitis in mice and induces *in vitro* generation of regulatory immune cells | 2019 | Marine Drugs | [17]. |
| 13 | Echinochrome A promotes *ex vivo* expansion of peripheral blood-derived CD34(+) cells, potentially through downregulation of ROS production and activation of the Src-Lyn-p110delta pathway | 2019 | Marine Drugs | [18] |
| 14 | The protective effect of echinochrome A on extracellular matrix of vocal folds in ovariectomized rats | 2020 | Marine Drugs | [19] |
| 15 | Echinochrome A Treatment Alleviates Atopic Dermatitis-like Skin Lesions in NC/Nga Mice via IL-4 and IL-13 Suppression. | 2021 | Marine Drugs | [20] |
| 16 | Echinochrome A protects against ultraviolet B-induced photoaging by lowering collagen degradation and inflammatory cell infiltration in hairless mice | 2021 | Marine Drugs | [21] |

End of Table 2

| | Title | Year | Journal | Reference |
|---|---|---|---|---|
| 17 | Echinochrome A treatment alleviates fibrosis and inflammation in bleomycin-induced scleroderma | 2021 | Marine Drugs | [22] |
| 18 | Multifaceted clinical effects of echinochrome | 2021 | Marine Drugs | [23] |
| 19 | Regulation of inflammation-mediated endothelial to mesenchymal transition with echinochrome A for improving myocardial dysfunction | 2022 | Marine Drugs | [24] |
| 20 | Echinochrome A inhibits melanogenesis in B16F10 cells by downregulating CREB signaling. | 2022 | Marine Drugs | [25] |
| 21 | Implication of echinochrome A in the plasticity and damage of intestinal epithelium. | 2022 | Marine Drugs | [26] |
| 22 | Effect of echinochrome A on submandibular gland dysfunction in ovariectomized rats | 2022 | Marine Drugs | [27] |
| 23 | Echinochrome prevents sulfide catabolism-associated chronic heart failure after myocardial infarction in mice | 2023 | Marine Drugs | [28] |
| 24 | Physicochemical characterization and phase II metabolic profiling of echinochrome A, a bioactive constituent from sea urchin, and its physiologically based pharmacokinetic modeling in rats and humans | 2023 | Biomed Pharmacother | [29] |
| 25 | Multiple effects of echinochrome A on selected ion channels implicated in skin physiology. | 2023 | Marine Drugs | [30] |
| 26 | Echinochrome A prevents diabetic nephropathy by inhibiting the PKC-Iota pathway and enhancing renal mitochondrial function in db/db mice | 2023 | Marine Drugs | [31] |

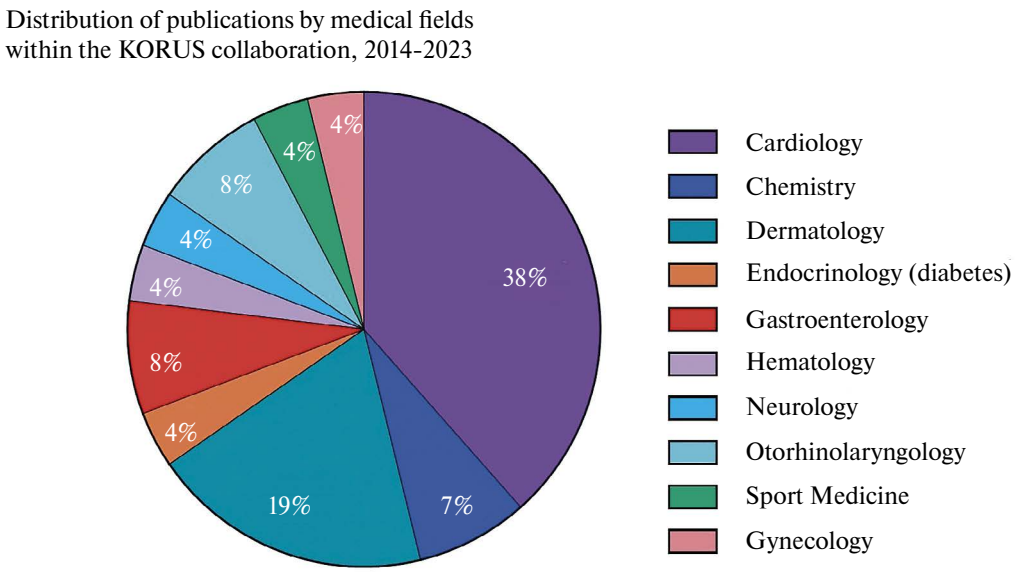


Fig. 4. Distribution of publications by medical fields within the KORUS collaboration, 2014–2023

### 4.1. Marine triterpene glycosides

First, together with Dr. Kwak, we investigated the triterpene glycosides from sea cucumbers, relying on Dr. Stonik's expertise in this field: frondoside A, cucumarioside $A_2$-2, stichoposide C (STC) and stichoposide D (STD) (Figure 5). Triterpene glycosides can induce membranolytic effects, including degradation of barrier function, increase in membrane permeability and ultimately rupture of cell membranes. In particular, frondoside A and cucumarioside exhibited cytotoxic effects on cancer cells by inhibiting tumorigenesis and metastasis while modulating the anti-tumor immune response in cancer cells. After characterizing the compounds isolated from the holothurians and sea urchins, we have studied in detail their anticancer activity. Jin et al. [32] found both frondoside A and cucumarioside $A_2$-2 to induce apoptosis in leukemic cells. Among the two compounds, frondoside A has faster response and potency compared to cucumarioside $A_2$-2. Notably, cucumarioside $A_2$-2 induced apoptosis dependent on the caspase cascade pathway. This suggests that holothurian-derived compounds may induce apoptosis in leukemic cells either independently or dependent on the caspase cascade depending on the structure of the holothurian compounds. Similarly, STC and STD show anticancer effects by generating ceramide but each compound uses different mechanisms of action to fight cancer [33]. In a study using STC, Yun et al. [34] determined the mechanism that induces apoptosis in leukemia and colorectal cancer cells. Dose-dependent treatment with STC activated mitochondrial damage and Fas, caspase-3 and caspase-8, which are key pro-apoptotic proteins. Conversely, it activated sphingomyelinase (SMase) and neutral SMase resulting in the generation of ceramide. Similarly, the STD also activated Fas where it translocated to lipid rafts and mediated cell apoptosis in leukemia xenografts [35]. The results suggest that STD activates SMase, thereby enabling *de novo* synthesis of ceramide as observed during STC treatment. (Figure 6.)

Fig. 5. Prof. Stonik with the Korean Team including Dr. Kwak from Ajou University, working on marine triterpene glycosides

We also investigated other marine triterpene glycosides specifically cladoloside $C_2$ and holotoxin $A_1$ from the holothurian *Cladolabes schmeltzii.* Cladoloside $C_2$, similar to STC and STD, had a dose- and time-dependent treatment that was able to induce apoptosis in leukemia cells and xenograft models. However, cladoloside $C_2$, induces apoptosis through an extrinsic pathway going through the

Fig. 6. Dr. Hwayoung Yun of Pusan National University leads the physicochemical study to characterize Ech A

activation of Fas, ceramide, caspase-8 but also the p38 kinase/c-Jun-NH2-terminal (JNK) pathway in lipid rafts [36]. Holotoxin $A_1$ is a more potent inducer of apoptosis activating caspase-8 and caspase-3 compared to cladoloside $C_2$. Taken together, our results suggest that the structure-activity relationship of marine triterpene glycosides can be applied to the development of new anticancer drugs. Future studies incorporate our findings and investigate treatment-resistant phenotypes and other types of cancer using these highlighted marine compounds.

### 4.2. Spinochrome pigments

Under the KORUS partnership, we have extensively studied polyhydroxynaphthoquinone echinochrome A (Ech A), a natural naphthoquinone pigment from the sea urchin *Scaphechinus mirabilis*. Ech A was developed by PIBOC and successfully patented in Russia, Republic of Korea and the United States. The crystalline form of Ech A has a dark red color and is soluble in alcohol. It is also minimally soluble in chloroform but insoluble in water. Commercially, it is an active

Ech A has shown cardioprotective, anticancer, antidiabetic, and antiviral activities. We have established a physiologically based pharmacokinetic model to support its potential clinical application [29]. Our results suggest that Ech A forms four possible metabolites in the liver and is eliminated by hepatic metabolism. Our model simulations also show that Ech A does not accumulate in systemic and local tissues after treatment and can be used to predict drug-drug interactions to optimize dosage regimens and drug formulations. Given this, we have then conducted experiments on Ech A in various medical fields (Figure 7).

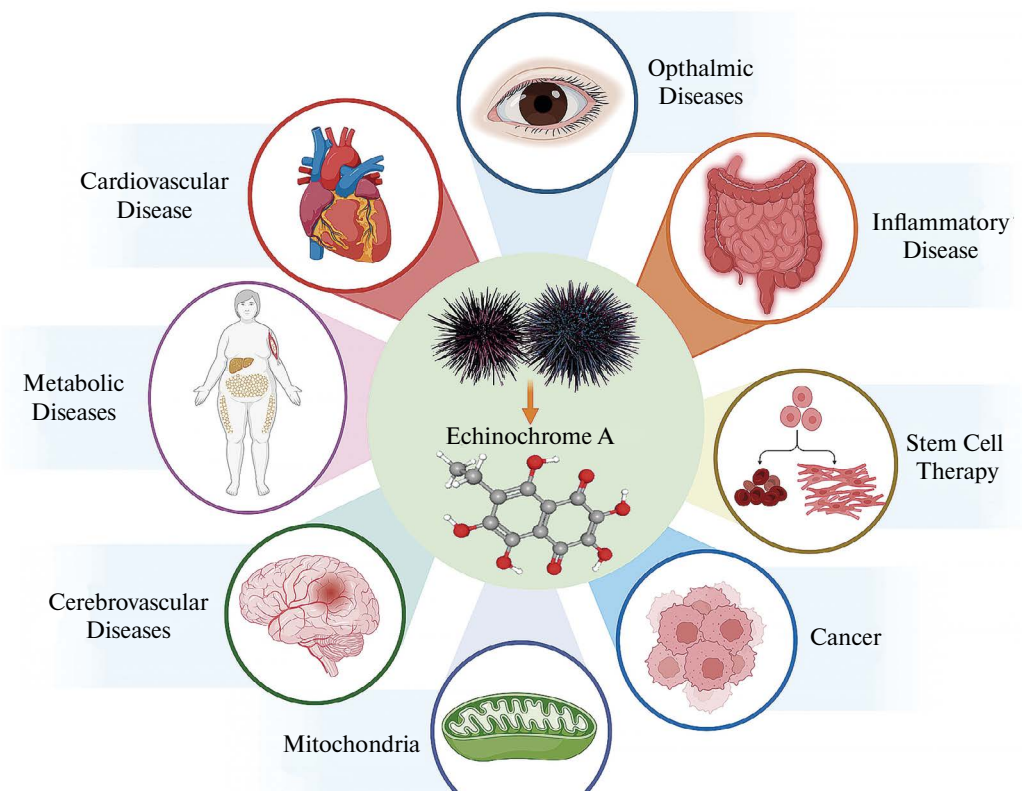


Fig. 7. Echinochrome A is a versatile compound that has the potential to treat various diseases through multiple mechanisms and modes of treatment. Images rendered by Biorender.com. Use of the images is subject to BioRender's Academic License Terms

### 4.2.1. Hematology

In our blood-related studies, we have found that Ech A confers protection and regulation of immune and blood cells. The study of Park et al [18] showed that Ech A suppressed reactive oxygen species (ROS) in peripheral blood $CD34^+$ cells and modulated p38/JNK activation. This also affected the ability of $CD34^+$ cells to expand. This suggests that Ech A can potentially rescue the proliferation and differentiation activity of hematopoietic stem cells and progenitor cells. Taken together, these results suggest that, Ech A may be incredibly useful in the treatment of blood-borne and inflammatory diseases (Figure 8).

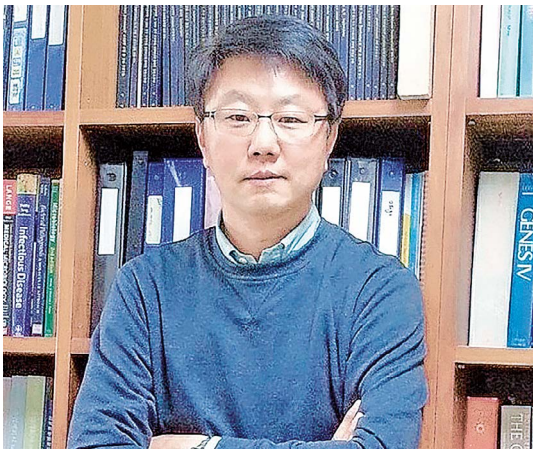

Fig. 8. Prof. Jee-Yeong Jeong of Kosin University College of Medicine led the hematology-focused research on Ech A

### 4.2.2. Otorhinolaryngology

The antioxidant properties of Ech A make it a versatile compound that can be applied to a variety of medical fields. Due to its structure, Ech A has a high capacity to scavenge free radicals and thus, can improve ECM composition. In this study, Kim et al. [19] have demonstrated the therapeutic potential of Ech A on the alteration of extracellular matrix (ECM)-related genes that can be affected by sex hormones when female rates are ovariectomized. The changes in the larynx, as well as vocal fold and voice are closely related to the level of sex hormones that fluctuate with the menstrual cycle during reproductive years. Voice production relies on the ECM of vocal fold tissues; therefore, a decrease in estrogen, such as menopause, can cause dysfunction due to ECM degradation. In this study, simulated estrogen deficiency via ovariectomy resulted in decreased MMP expression, but subsequent Ech A treatment led to amelioration. However, ECM components remained unchanged in both Ech A-treated and untreated groups. Interestingly, Collagen I and III levels were significantly increased in the Ech A treated groups. These results suggest that Ech A may have protective effects on the ECM of vocal fold tissues. In connection to this, Kim et al. [27] then observed submandibular gland dysfunction in ovariectomized rats to mimic and its related postmenopausal dry mouth syndrome. Ech A treated groups had incidence of ferroptosis, decreased inflammation and fibrosis. These groups also had improved submandibular gland functions suggesting that Ech A may be a potential therapeutic drug to mitigate sex hormone-related otolaryngologlogical concerns (Figure 9).

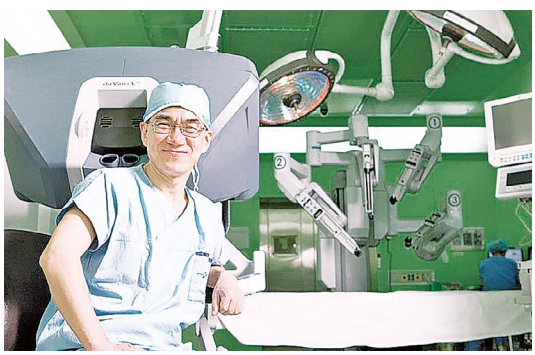

Fig. 9. Dr. Byoung-Joo Lee of Pusan National University leads the study of Ech A application in otorhinolaryngology

### 4.2.3. Gynecology

The anti-inflammatory and antioxidant properties of Ech A make it potentially suitable for the treatment of pre-eclampsia (PE) [37]. Immune dysregulation occurs during PE and is a leading cause of maternal and neonatal morbidity and mortality worldwide. Sprague-Dawley

Fig. 10. Dr. Yinhua Zhang from Seoul National University leads Ech A studies focused on gynecology

gestation day (GD) 7 pregnant rats were treated with Ech A alone from GD 14 and co-treatment with angiotensin II (Ang II) at GD8 followed by Ech A treatment at GD 14. All treatments were performed until GD20. Results showed that Ang II increased blood pressure but decreased fetal and placental weight. It also decreased glomeruli and associated capillary size. Ech A treatment reduced blood pressure and improved glomerular morphology while placental and fetal parameters remained unchanged. Inflammatory markers such as TNF-α increased, while IL-10 and VEGF decreased with Ang II treatment. These marker expressions were reversed and restored by Ech A treatment. Ang II treatment reduced B-cell lymphoma 2 (Bcl-2) expression and Bcl-2/BCL2-associated X (Bax) ratio in the kidney and heart, which were significantly reversed by Ech A. Based on the evidence, Ech A attenuates inflammation and apoptosis in key organs while also preserving organ structure and improving blood pressure (Figure 10).

### 4.2.4. Gastroenterology

Given that Ech A has been shown to have anti-inflammatory properties, we also investigated its therapeutic potential for inflammatory bowel disease (IBD) using a murine colitis-induced model [17]. Intravenous injection of Ech A showed significant prevention of body weight loss and lethality. Ech A was also able to maintain homeostasis *in vivo.* Of note, Ech A stimulated generation of regulatory T cells that modulated the inflammatory response but inhibited T cell proliferation using naive $T_0$ cells. *In vitro* macrophage studies showed suppression of pro-inflammatory M1 macrophages. In contrast, Ech A induced the production of M2 macrophages, which function to resolve inflammation and initiate tissue repair. Overall, Ech A may be beneficial against IBD by attenuating intestinal homeostasis. In this context, Ahn et al. investigated the biosafety of orally administered Ech A and its influence on intestinal cells [26]. Intestinal and colonic epithelial organoids were treated with Ech A treatment. Afterwards, the expressions of LGR5 and MUC2, a marker of intestinal stem cells and goblet cells, respectively, showed a significant increase, as well as the revival stem cells, Ly6a and CLU. The results suggest that Ech A is safe for intestinal tissues

Fig. 11. Dr. Hyung-Sik Kim from Pusan National University leads research on gastroenterology

and may even promote the regeneration and maintenance of epithelium and may be potentially suitable for oral administration. (Figure 11.)

### 4.2.5. Endocrinology

Recently, we have started to investigate on the possible effects of Ech A on diabetic conditions and focused on the diabetic nephropathy model using seven-week-old obese db/db mice [31]. The results showed that Ech A improved diabetic conditions such as glucose tolerance and decreased blood urea nitrogen and creatinine. However, Ech A had no significant effect on body weight. Ech A also improved ATP production and conversely, decreased renal malondialdehyde and lipid hydroperoxide levels. We have also elucidated the mechanism of action of Ech A. As an antioxidant, Ech A rescues oxidative stress and fibrosis by inhibiting protein kinase C-iota (PKCι)/p38 mitogen-activated protein kinase, which downregulates phosphorylation of p53 and c-Jun. This study also found that Ech A treatment reduced kidney scarring and cell damage in diabetic mice by regulating transforming growth factor-beta 1 (TGFβ1) signaling. It also improved mitochondrial function in the kidneys by blocking the PKCι/p38 MAPK signaling pathway, which leads to fibrosis and oxidative stress. This was achieved by activating the AMPK/NRF2/HO-1 pathway, which protects the kidneys from damage. Our results suggest that Ech A can be used as a potential option against diabetic nephropathy (Figure 12).

Fig. 12. Prof. Hyoung Kyu Kim from Inje University investigated Ech A in Type 2 diabetic nephropathy

### 4.2.6. Neurology

Although medical technology has continuously advanced over time, interventions in patients with ischemic stroke still lead to serious consequences and high mortality. Kim et al. [16] found that Ech A had an antioxidant effect that ameliorated brain deterioration in Sprague-Dawley rats. Ech A treatment was able to partially restore the damaged brain area and behavior in rats. This is further supported by the expression of cell survival related molecules such as Bcl-2, caspase-3, Bax, ERK, AKT, and brain-derived neurotrophic factor (BDNF). Bcl-2, a key anti-apoptotic marker, increased, while caspase-3 and Bax decreased, as these are pro-apoptotic markers. ERK, AKT and BDNF increased, indicating that Ech A could relieve physiological damage in the rat model of cerebral ischemia (Figure 13).

Fig. 13. Prof. Woochul Chang of Pusan National University studies neurological benefits of Ech A

### 4.2.7. Dermatology

Ech A is known for its antioxidant and anti-inflammatory effects. The study by Seol et al. [21] determined the efficacy of Ech A against skin aging, which is largely dependent on oxidative stress. Hairless mice were exposed to ultraviolet B light for 8 weeks, but the group injected intraperitonially with Ech A showed improved skin conditions. This was because Ech A reduced transepidermal water loss and attenuated skin inflammation and collagen degeneration (Figure 14, 15). There was also a significant decrease in the expression of matrix metalloproteinase (MMP), mast cell-related proteins tryptase and chymase, suggesting the efficacy of Ech A through collagen degradation based on mast cells and MMP expression. Another study examined melanogenesis, which may be associated with skin aging, darkening and cancer. Choi et al. [25] used the B16F10 murine melanoma cell line treated with Ech A and found that Ech A blocked melanin synthesis through the CREB signaling pathway. These results suggest that Ech A can also be used in skin whitening formulations to prevent pigmentation.

Fig. 14. Dr. Jung Eun Seol of Inje University Busan Paik Hospital conducted research on photoaging and Ech A

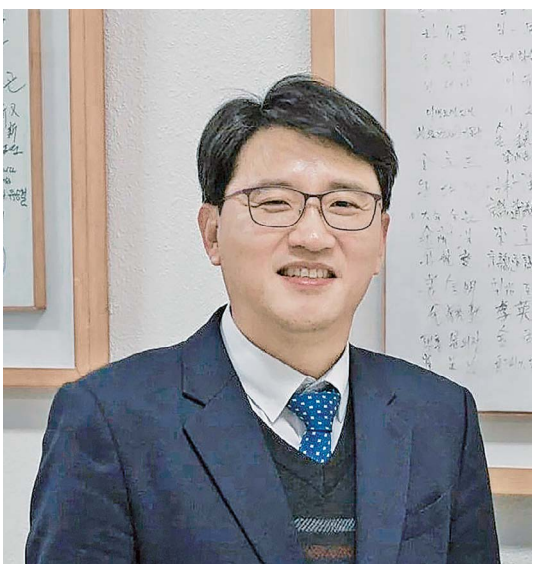

Fig. 15. Dr. Sang-Rae Lee from Inje University Busan Paik Hospital determined the effect of Ech A on melanogenesis

Ech A has also been found to alleviate atopic dermatitis (AD), which is largely due to inflammation and oxidation. Yun et al. [20] induced AD in NC/Nga mice using 2,4-dinitrochlorobenzene (DNCB), a known compound used to induce AD-like skin lesions co-treated with Ech A. The observed results showed that Ech A rescued DNCB-treated skin by reducing skin dryness, edema, and erythema. It also improved water retention and stratum corneum hydration. Inflammatory markers such as interferon-γ, interleukin-4, and interleukin-13 were also suppressed, confirming the anti-inflammatory efficacy of Ech A. Park et al. [22] also observed high efficacy of Ech A as an anti-inflammatory and anti-fibrotic drug in scleroderma (Figure 16). This study found that Ech A treatment reduced myofibroblast activation by decreasing the expression of α-SMA, vimentin, and phosphorylated Smad3, and also reduced macrophages, suggesting its anti-inflammatory effect. These findings have determined the biochemical signaling mechanisms of Ech A in skin diseases and have yet to provide insight into its pharmacological effects.

Ech A treated to HEK293 cells with overexpressing TRPV3, TRPV1 and Orai1

channels and the two-pore domain K+ (K2P) channels (TREK/TRAAK, TASK-1, and TRESK) were subjected to patch clamp technique to determine its pharmacological effects [30]. Inhibition was observed in TRPV3 and Orai1. On the other hand, TREK/TRAAK was activated under treatment with its chemical agonists and Ech A (Figure 17). The results suggest that Ech A may also act under a pharmacological mechanism making it a viable candidate for further investigation using ion channels and $Ca^{2+}$ signaling.

### 4.2.8. Cardiology

Previous findings demonstrated the cardioprotective properties of Ech A and we were able to identify several mechanisms for this effect. We inferred the protective effect of Ech A against toxic agents, specifically tert-butyl hydroperoxide (tBHP), sodium nitroprusside (SNP), and doxorubicin. These agents induce mitochondrial dysfunction as evidenced by increased ROS and decreased mitochondrial membrane potential. When rat cardiac myoblast H9c2 cells were exposed to cardiotoxic agents and treated with Ech A, we observed attenuation of membrane potential, ROS and adenosine triphosphate (ATP) levels even under toxic conditions [6] (Figure 18). Jeong et al. [7] further investigated the effect of Ech A on mitochondrial biogenesis and oxidative phosphorylation. Dose-dependent treatment with Ech A reduced ROS and did not affect cell viability. Ech A treatment improved mitochondrial biogenesis function as evidenced by increases in cellular oxygen consumption rate, mitochondrial ATP levels, and mitochondrial content. This is also complemented by the upregulation of mitochondrial biogenesis transcription genes, ultimately suggesting that Ech A can be used where mitochondria play a key role such as in heart disease. Ischemic heart disease is characterized by insufficient oxygen due to reduced blood supply resulting in myocardial stress. Acetylcholine (ACh) is a known cardioprotector, but acetylcholinesterase (AChE) can hydrolyze Ach and impair cardiac function. Lee et al. [8] investigated the anti-AChE effect of Ech A in H9c2 and A7r5 rat aortic vascular smooth muscle cells where Ech A showed an inhibitory effect on AChE. Ech A also inacti-

Fig. 16. Prof. Jae-Ho Kim from Pusan National University determined the effects of Ech A in scleroderma

Fig. 17. Prof. Sung Joon Kim investigated the effect of Ech A to ion channels in skin physiology

Fig. 18. Prof. Jin Han of Inje University leads studies on Ech A related to cardiovascular disease and physiolog.

Fig. 19. Dr. Sang Hong Baek from Seoul St. Mary's Hospital of the Catholic University of Korea determined the effect of Ech A in cardiac progenitor cells

vated ROS Ech A also inactivated ROS, particularly nitric oxide. The results suggest the therapeutic potential of Ech A in other disease models that may be driven by AChE. In this regard, Kim et al. [9] specifically determined the effects of Ech A on cardiac excitation-contraction in the Wistar rat heart model and established its modulation of $Ca^{2+}$. Ech A treatment showed inotropic effects like (inherent to) AChE inhibitors, but Ech A did not show other effects as AChE inhibitors. We also identified SERCA2A as a possible target of Ech A based on its dephosphorylation of phospholamban Ser16. In addition, we observed that Ech A attenuated myocardial infarction in ischemic/reperfused hearts compared to untreated hearts, and that $Ca^{2+}$ modulation appeared to be independent of the antioxidant properties of Ech A. Overall, the findings strengthen our understanding of Ech A as a modulator of $Ca^{2+}$ and possibly, myocardial infarction (MI). Investigating the effect of Ech A on heart failure related to sulfide catabolism, Tang et al. [28] has also demonstrated that Ech A has the potential to improve cardiac conditions after MI. Their results showed that continuous Ech A treatment modulated left ventricular systolic dysfunction and prevented structural remodeling after MI. Ech A suppressed reactive sulfur species (RSS) and reduced MI-induced oxidative stress formation (Figure 18).

Another study further established the effect of Ech A on endothelial–mesenchymal transition (EndMT) as a reparative mechanism that attenuates myocardial infarction. *In vitro* and *in vivo* results show that Ech A negatively regulates early EndMT, thereby reducing the myofibroblast and fibrotic area suggesting its potential therapeutic significance for cardioprotection or regeneration [24]. Kim et al. [13] have also investigated the potential of Ech A to enhance cardiomyocyte differentiation by also examining mitochondrial membrane potential, mitochondrial mass and ROS generation, but this time using mouse embryonic stem cells (mESC) of the EMG7 line. Ech A treatment increased differentiation with higher beating rates as well as increased mitochondrial mass and membrane potential. This study complemented by computational protein-ligand docking simulation and surface plasmon resonance results, also determined Ech A to significantly decrease protein kinase C-iota (PKCι), suggest-

ing the direct binding of Ech A to PKCι and inhibiting its activity. Since Ech A is insoluble in water, we also investigated a drug based on Ech A and known as Histochrome, which during medical application has been shown to reduce myocardial ischemic injury. The study of Park et al. [15] determined the cardioprotective effect of Histochrome on patient-derived cardiac progenitor cells (CPCs) (Figure 19**)**. CPCs play a role in the repair of ischemic heart tissue, and we found that pretreatment of CPCs with Histochrome resulted in significant upregulation of the anti-apoptotic proteins Bcl-2 and Bcl-xL, while suppressing the pro-apoptotic proteins Bax, caspase-3, and phosphorylated histone (γH2A.X) foci. Histochrome treatment also prolonged the viability of CPCs and prevented the accumulation of oxidative stress. This demonstrates that Histochrome is a viable candidate as a biosafe cell preconditioning agent in CPCs for the treatment of heart disease. Taken together, our results suggest that treatment with Ech A and drug Histochrome may be used as a novel therapeutic modality for the treatment of cardiac ischaemia/reperfusion (I/R) and heart disease in general.

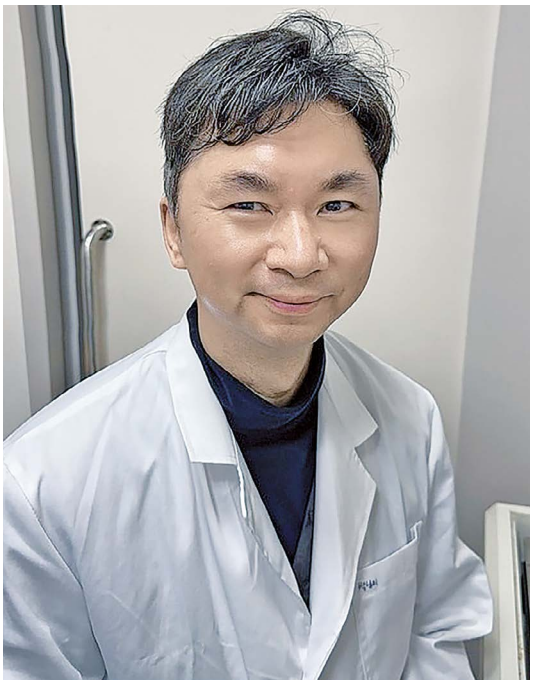

Fig. 20. Dr. Chang Shin Yoon of Inje University studied the cardioprotective effect of SpD

We have also experimented with and successfully patented spinochrome D (SpD), a structural analog of Ech A, which is an active component of the well-known cardioprotective drug Histochrome. The abundance of SpD in sea urchins is low, but our partners in PIBOC have developed a synthesis scheme to increase its yield. Given the established cardioprotective effects of Ech A, we reasoned that a SpD might show similar results. Yoon et al. [12] used metabolomics and mass spectrometry-based proteomics to characterize proteins and metabolites induced by SpD in the human cardiomyocyte cell line AC16 and the human breast cancer cell line MCF-7. (Figure 20.) Metabolic and proteomic analyses show that SpD treatment significantly enhances glutathione metabolism, especially in AC16 cells. Co-treatment of SpD with the known anticancer drug Doxorubicin attenuated the cytotoxicity without compromising the anticancer efficacy of Doxorubicin on the system. Of note, there is a significant difference in mitochondrial membrane potential and mitochondrial calcium localization between AC16 and MCF-7 cells. In another study, we also compared seven other echinochrome analogs co-treated with Doxorubicin in AC16 cells.

Our results showed that these analogues also confer cardioprotective effects, with enhanced antioxidant activity and ATP production, suggesting that structural analogues of Ech A may be a potential therapeutic agents against cardiovascular disease [14].

### 4.2.9. Sports Medicine

Previous studies have shown that bioactive compounds from marine organisms can improve recovery after exercise. As mentioned above, Ech A supplementation improved mitochondrial function in cardiac muscle, so our collaborative studies hypothesized that Ech A might lead to an improvement in exercise capacity, which was focus on skeletal muscle of Sprague-Dawley rats [11]. We found that Ech A treatment lowered the body weight of the rats, but the mitochondrial content of the gastrocnemius muscle was significantly increased in both the non-exercise and exercise groups with Ech A. Our results suggest that Ech

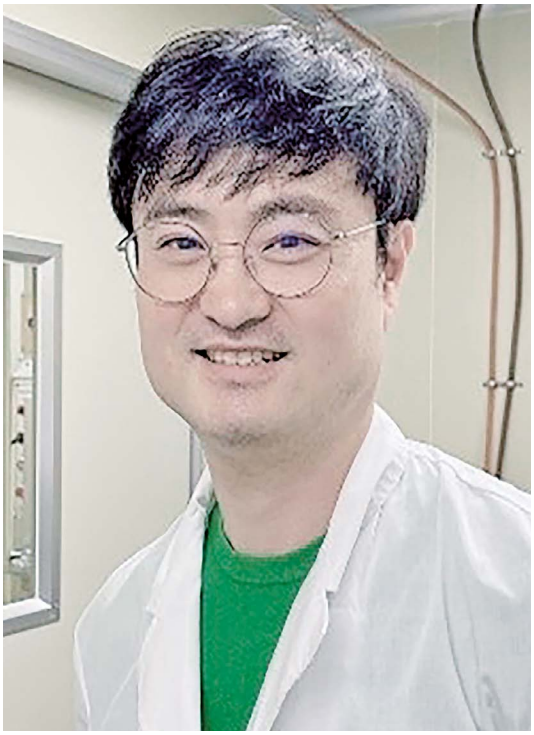

Fig. 21. Dr. Dae Yoon Seo lead the study on effect of Ech A in exercise capacity

Fig. 22. Drs. Nikolay E. Nifantiev, Valentin A. Stonik and Tatyana N. Makarieva collaborated on NPS A

A administration may improve exercise capacity as associated with an increase in mitochondrial content in skeletal muscle (Figure 21).

### 4.3. Neopetroside A

One of the milestones of our collaboration was the successful patenting of the marine compound Neopetroside (NPS) A and B in Korea. This natural product was extracted from the sea sponge genus Neopetrosia, which is rich in bioactive metabolites that exhibit a wide range of biological activities, such as cytotoxic effects against cancer cells and inhibitory effects under various conditions [10]. Recently, we were able to determine its efficacy against cardiovascular injury, particularly myocardial I/R injury. *In vivo* and *in vitro* experiments were performed to determine the effect of NPS A on the heart. We found that NPS A is non-toxic to both models, with NPS decreasing to 10% of its initial concentration *in vivo*, remaining non-toxic and without altering single cell contractility *in vitro*. *In an ex vivo* Langendorff perfusion system, we observed the reduction of I/R injury with NPS A, which improved left ventricular pressure and cardiac function after the treatment. In addition, NPS A treated hearts showed significantly smaller infarct size and reduced ROS levels, suggesting that NPS A preserves hemodynamic status and suppresses ROS generation. Next, *in vitro* kinase assay targeting energy metabolism pathways in the presence of NPS A where we found 69 kinases and observed reduced kinase activity of GSK-3β. Further investigation revealed that the cardiac effects were due to inhibition of GSK-3β, which regulates nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide ($NAD^+$/NADH) through activation of the nuclear factor erythroid 2–related factor 2/NAD(P)H quinone oxidoreductase 1 (Nrf2/Nqo1) axis in a phosphorylation-independent manner. Our findings suggest NPS A treatment may be a potential pharmacologic intervention modality for cardiac I/R injury and subsequent prevention of heart failure (Figure 22).

The study of marine natural products can provide cutting-edge knowledge that can later be translated into new treatment modalities, and we collectively hope to contribute to this body of knowledge in the years to come.

## 5. Future Prospects

The results of Korean-Russian collaboration have repeatedly proven that the joint work of scientists from different countries with different cultures and experiences creates an excellent atmosphere of creativity in each of our unique scientific laboratories, successfully complementing the efforts of everyone. This research environment is conducive to solving new revolutionary problems in our chosen fields. However, we still have the obstacles to overcome, such as:

- **Lack of available information:** The medical community and the general public are not sufficiently aware of the potential benefits of marine natural products, which is the main impetus for our collaboration. Lack of information can make it difficult to apply for funding for research and development that could bridge the gap between marine biotechnology and medical applications [38].
- **High cost of research:** Collecting samples of marine organisms can be costly and complicated, especially for organisms that live at depth and in hostile environments. Expeditions for marine research and data collection can be expensive because of the need to ensure the safety of researchers and the quality of collections.
- **Regulatory limitations:** Successful research can ultimately lead to real products, but the approval of new drugs goes through rigorous procedures that cost time and money. Marine drugs may be considered "new chemical entities", and rigorous testing is required, especially as they begin to move from "bench to bed", i.e., from the laboratory to human clinical applications [39].
- **Sustainability:** As with most natural resources, a number of marine organisms that can be harvested is finite and we need to save wild populations so they can thrive in the environment. The disturbance of the marine environment during expeditions for sample collection is undoubtedly a negative impact. We must always ensure that there is minimal damage to the environment and prevent overexploitation of marine resources [40].

Despite these challenges, the potential benefits of marine biotechnology in healthcare are significant. Further research and development in marine biotechnology has the potential to revolutionize healthcare and improve the lives of millions of people.

We are committed to maintaining and expanding close relationships with our partner institutions to further enhance our research results. We remain optimistic that with the results of the basic research, as well as the successfully obtained patents, we can continue our way towards advanced clinical trials of the marine natural products we have synthesized and tested in specific disease models.

## 6. Conclusion

Since 1993 to date, the fruitful collaboration under 19 agreements between PIBOC and 17 Korean institutes covering a wide area of Korea has yielded significant results. Based on the experience of Russian and Korean scientists, we have made many great achievements in various scientific fields, such as the research of marine natural products for biochemistry, microbiology, pharmacology, as well as for their applications in medicine, focusing on cardiovascular diseases.

As members of the "KORUS-MUSIC Orchestra", we will continue to create beautiful "symphonies" together, which may be different, but are complementary to each other and always in harmony with the emerging cutting-edge trends.

## Funding

This work was supported by the Basic Research Laboratory program and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Korean government (RS-2023-00270463 and RS-2023-00221673) and by Korea Basic Science Institute (National Research Facilities and Equipment Center) grant funded by the Ministry of Education (2023RIA6C101B008).

СПИСОК ИСТОЧНИКОВ

1. Banerjee P., Mandhare A., Bagalkote V. Marine natural products as source of new drugs: an updated patent review (July 2018–July 2021) // Expert Opinion on Therapeutic Patents. 2022. Vol. 32, N. 3. P. 317–363.

2. Sigwart J.D., Blasiak R., Jaspars M., Jouffray J.-B., Tasdemir D., Unlocking the potential of marine biodiscovery // Nat. Prod. Reports. 2021. Vol. 38, N. 7. P. 1235–1242.

3. Rotter A., Bacu A., Barbier M., Bertoni F., Bones A.M., Cancela, M.L., Carlsson J., Carvalho, M.F., Cegłowska M., Dalay M.C. A new network for the advancement of marine biotechnology in Europe and beyond // Front. Mar. Sci. 2020. Vol. 7. Art. 278. https://doi.org/10.3389/fmars.2020.00278.

4. Haque N., Parveen S., Tang T., Wei J., Huang Z. Marine natural products in clinical use // Mar. Drugs. 2022. Vol. 20, N. 8. Art. 528 [1–40].

5. Donia M., Hamann M.T. Marine natural products and their potential applications as anti-infective agents // Lancet Infect. Diseas. 2003. Vol. 3, N. 6. P. 338–348.

6. Jeong S.H., Kim H.K., Song I.S., Lee S.J., Ko K.S., Rhee B.D., Kim N., Mishchenko N.P., Fedoryev S.A., Stonik, V.A., Han J. Echinochrome A protects mitochondrial function in cardiomyocytes against cardiotoxic drugs // Mar. Drugs. 2014. Vol. 12, N. 5. P. 2922–2936.

7. Jeong S.H., Kim H.K., Song I.S., Noh S.J., Marquez J., Ko K.S., Rhee B.D., Kim N., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome a increases mitochondrial mass and function by modulating mitochondrial biogenesis regulatory genes // Mar. Drugs. 2014. Vol. 12, N. 8. P. 4602–4615.

8. Lee S.R., Pronto J.R., Sarankhuu B.E., Ko K.S., Rhee B.D., Kim N., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Acetylcholinesterase inhibitory activity of pigment echinochrome A from sea urchin *Scaphechinus mirabilis* // Mar. Drugs. 2014. Vol. 12, N. 6. P. 3560–3573.

9. Kim H.K., Youm J.B., Jeong S.H., Lee S.R., Song I.S., Ko T.H., Pronto J.R., Ko K.S., Rhee B.D., Kim N., Nilius B., Mischchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome A regulates phosphorylation of phospholamban Ser16 and Thr17 suppressing cardiac SERCA2A $Ca^{2+}$ reuptake // Pflugers Arch. 2015. Vol. 467, N. 10. P. 2151–2163.

10. Shubina L.K., Makarieva T.N., Yashunsky D.V., Nifantiev N.E., Denisenko V.A., Dmitrenok, P.S., Dyshlovoy S.A., Fedorov S.N., Krasokhin V.B., Jeong S.H., Han J., Stonik V.A. Pyridine nucleosides neopetrosides A and B from a marine *Neopetrosia* sp. sponge. Synthesis of neopetroside A and its β-riboside fnalogue // J. Nat. Prod. 2015. Vol. 78, N. 6. P. 1383–1389.

11. Seo D.Y., McGregor R.A., Noh S.J., Choi S.J., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome A improves exercise capacity during short-term endurance training in rats // Mar. Drugs. 2015. Vol. 13, N. 9. P. 5722–5731.

12. Yoon C.S., Kim H.K., Mishchenko N.P., Vasileva E.A., Fedoreyev, S.A., Stonik V.A., Han J. Spinochrome D attenuates doxorubicin-induced cardiomyocyte death via improving glutathione metabolism and attenuating oxidative stress // Mar. Drugs. 2018. Vol. 17, N. 1. Art. 2 [1–20].

13. Kim H.K., Cho S.W., Heo H.J., Jeong S.H., Kim M., Ko K.S., Rhee B.D., Mishchenko N.P., Vasileva E.A., Fedoreyev S.A., Stonik V.A., Han J. A novel atypical PKC-Iota inhibitor, echinochrome A, enhances cardiomyocyte differentiation from mouse embryonic stem cells // Mar. Drugs. 2018. Vol. 16, No. 6. Art. 192 [1–14].

14. Yoon C.S., Kim H.K., Mishchenko N.P., Vasileva E.A., Fedoreyev S.A., Shestak O.P., Balaneva N.N., Novikov V.L., Stonik V.A., Han J. The protective effects of echinochrome A structural analogs against oxiative stress and doxorubicin in AC16 cardiomyocytes // Mol. Cell. Toxicol. 2019. Vol. 15. P. 407–414.

15. Park J.H., Lee N.K., Lim H.J., Mazumder S., Rethineswaran K.V., Kim Y.J., Jang, W. B.; Ji S.T., Kang S., Kim D.Y., Van L.T.H., Giang L.T.T., Kim D.H., Ha J.S., Yun J., Kim H., Han J., Mishchenko N.P., Fedoreyev S.A., Vasileva E.A., Kwon S.M., Baek S.H. Therapeutic cell protective role of histochrome under oxidative stress in human cardiac progenitor cells // Mar. Drugs. 2019. Vol. 17, N. 6. Art. 368 [1–15].

16. Kim R., Hur D., Kim H.K., Han J., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Chang W. Echinochrome A attenuates cerebral ischemic injury through regulation of cell survival after middle cerebral artery occlusion in rat // Mar. Drugs. 2019. Vol. 17, N. 9. Art. 501 [1–8].

17. Oh S.J., Seo Y., Ahn J.S., Shin Y.Y., Yang J.W., Kim H.K., Han J., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.S. Echinochrome A reduces colitis in mice and induces *in vitro* generation of regulatory immune cells // Mar. Drugs. 2019. Vol. 17. N. 11. Art. 622 [1–10].

18. Park G.B., Kim M.J., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J., Lee H.S., Kim D., Jeong J.Y. Echinochrome A promotes *ex vivo* expansion of peripheral blood-derived

CD34(+) cells, potentially through downregulation of ROS production and activation of the Src-Lyn-p110δ pathway // Mar. Drugs. 2019. Vol. 17, N. 9. Art. 526 [1–14].

19. Kim J.M., Kim J.H., Shin S.C., Park G.C., Kim H.S., Kim K., Kim H.K., Han J., Mishchenko N.P., Vasileva E.A., Fedoreyev S.A., Stonik V.A., Lee B.J. The protective effect of echinochrome A on extracellular matrix of vocal folds in ovariectomized rats // Mar. Drugs. 2020. Vol. 18, N. 2. Art. 77 [1–15].

20. Yun H.R., Ahn S.W., Seol B., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J., Ko K.S., Rhee B.D., Seol J.E., Kim H.K. Echinochrome A treatment alleviates atopic dermatitis-like skin lesions in NC/Nga mice via IL-4 and IL-13 suppression // Mar. Drugs. 2021. V. 19, N. 11 Art. 622 [1–11].

21. Seol J.E., Ahn S.W., Seol B., Yun H.R., Park N., Kim H.K., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome A protects against ultraviolet B-induced photoaging by lowering collagen degradation and inflammatory cell infiltration in hairless mice // Mar. Drugs. 2021. Vol. 19, N. 10. Art. 550 [1–13].

22. Park G.T., Yoon J.W., Yoo S.B., Song Y.C., Song P., Kim H.K., Han J., Bae S.J., Ha K.T., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim M.B., Kim J.H. Echinochrome A treatment alleviates fibrosis and inflammation in bleomycin-induced scleroderma // Mar. Drugs. 2021. Vol. 19, N. 5. Art. 237 [1–11].

23. Kim H.K., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Han J., Multifaceted clinical effects of echinochrome // Mar. Drugs. 2021. Vol. 19, N. 8. Art. 412 [1–16].

24. Song B.W., Kim S., Kim R., Jeong S., Moon H., Kim H., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Lee M.Y., Kim J., Kim H.K., Han J., Chang W. Regulation of inflammation-mediated endothelial to mesenchymal transition with echinochrome A for improving myocardial dysfunction // Mar. Drugs. 2022. Vol. 20, N. 12. Art. 756 [1–17].

25. Choi M.R., Lee H., Kim H.K., Han J., Seol J.E., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Ju W.S., Kim D.J., Lee S.R., Echinochrome A inhibits melanogenesis in B16F10 cells by downregulating CREB signaling // Mar. Drugs. 2022. Vol. 20, N. 9. Art. 555 [1–12].

26. Ahn J.S., Shin Y.Y., Oh S.J., Song M.H., Kang M.J., Park S.Y., Nguyen P.T., Nguyen, D. K., Kim H.K., Han J., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Seo Y., Lee B.C., Kim H.S. Implication of echinochrome A in the plasticity and damage of intestinal epithelium // Mar Drugs. 2022, No. 20, N. 11. Art. 715 [1–14].

27. Kim J.M., Shin S.C., Cheon Y.I., Kim H.S., Park G.C., Kim H.K., Han J., Seol J.E., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Lee B.J., Effect of echinochrome A on submandibular gland dysfunction in ovariectomized rats // Mar. Drugs. 2022. Vol. 20, N. 12. Art. 729 [1–14].

28. Tang X., Nishimura A., Ariyoshi K., Nishiyama K., Kato Y., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.K., Han J., Kanda Y., Umezawa K., Urano Y., Akaike T., Nishida M. Echinochrome prevents sulfide catabolism-associated chronic heart failure after myocardial infarction in mice // Mar. Drugs. 2023. Vol. 21, N. 1. Art. 52 [1–17].

29. Han D.G., Kwak J., Choi E., Seo S.W., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.K., Han J., Byun J.H., Jung I.H., Yun H., Yoon I.S. Physicochemical characterization and phase II metabolic profiling of echinochrome A, a bioactive constituent from sea urchin, and its physiologically based pharmacokinetic modeling in rats and humans // Biomed. Pharmacother. 2023. Vol. 162. Art. 114589 [1–16].

30. Kim S.E., Chung E.D.S., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.K., Nam J.H., Kim S.J. Multiple effects of echinochrome A on selected ion channels implicated in skin physiology // Mar. Drugs. 2023. Vol. 21, No. 2. Art. 78 [1–16]

31. Pham T.K., Nguyen T.H.T., Yun H.R., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Vu T.T., Nguyen H.Q., Cho S.W., Kim H.K., Han J. Echinochrome A prevents diabetic nephropathy by inhibiting the PKC-iota pathway and enhancing renal mitochondrial function in db/db mice // Mar. Drugs. 2023. Vol. 21, N. 4. Art. 222 [1–15].

32. Jin J.O., Shastina V.V., Shin S.W., Xu Q., Park J.I., Rasskazov V.A., Avilov S.A., Fedorov, S.N., Stonik V.A., Kwak J.Y., Differential effects of triterpene glycosides, frondoside A and cucumarioside $A_2$-2 isolated from sea cucumbers on caspase activation and apoptosis of human leukemia cells // FEBS Lett. 2009. Vol. 583, N. 4. P. 697–702.

33. Park J.I., Bae H.R., Kim C.G., Stonik V.A., Kwak J.Y., Relationships between chemical structures and functions of triterpene glycosides isolated from sea cucumbers // Front. Chem. 2014. Vol. 2. Art. 77 [1–14].

34. Yun S.H., Park E.S., Shin, S.W., Na Y.W., Han J.Y., Jeong J.S., Shastina V.V., Stonik V.A., Park J.I., Kwak J.Y. Stichoposide C induces apoptosis through the generation of ceramide in leukemia and colorectal cancer cells and shows in vivo antitumor activity // Clin. Cancer Res. 2012. Vol. 18, N. 21. P. 5934–5948.

35. Yun S.H., Park E.S., Shin S.W., Ju M.H.; Han, J.Y., Jeong J.S., Kim S.H., Stonik V.A., Kwak J.Y., Park J.I. By activating Fas/ceramide synthase 6/p38 kinase in lipid rafts, stichoposide D inhibits growth of leukemia xenografts // Oncotarget. 2015. Vol. 6, N. 29. P. 27596–27612.

36. Yun S.H., Sim E.H., Han S.H., Kim T.R., Ju M.H., Han J.Y., Jeong J.S., Kim S.H., Silchenko A.S., Stonik V.A., Park J.I. *In vitro* and *in vivo* anti-leukemic effects of cladoloside $C_2$ are mediated by activation of Fas/ceramide synthase 6/p38 kinase/c-Jun $NH_2$-terminal kinase/caspase-8 // Oncotarget. 2018 Vol. 9, N. 1. P. 495–511.

37. Cui H., Liu J., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Zhang, Y., Echinochrome A reverses kidney abnormality and reduces blood pressure in a rat model of preeclampsia // Mar. Drugs. 2022. Vol. 20, N. 11. Art. 722 [1–13].

38. Daniotti S., Re I. Marine biotechnology: challenges and development market trends for the enhancement of biotic resources in industrial pharmaceutical and food applications. A statistical analysis of scientific literature and business models // Mar. Drugs. 2021. Vol. 19. N. 2. Art. 61 [1–35].

39. Lindequist U. Marine-derived pharmaceuticals–challenges and opportunities // Biomol. Ther. 2016. Vol. 24, N. 6. 561–571.

40. OECD, Marine Biotechnology and the Bioeconomy. Paris: OECD, 2012.

## REFERENCES

1. Banerjee P., Mandhare A., Bagalkote V. Marine natural products as source of new drugs: an updated patent review (July 2018–July 2021) // Expert Opinion on Therapeutic Patents. 2022. Vol. 32, N. 3. P. 317–363.

2. Sigwart J.D., Blasiak R., Jaspars M., Jouffray J.-B., Tasdemir D., Unlocking the potential of marine biodiscovery // Nat. Prod. Reports. 2021. Vol. 38, N. 7. P. 1235–1242.

3. Rotter A., Bacu A., Barbier M., Bertoni F., Bones A.M., Cancela, M.L., Carlsson J., Carvalho, M.F., Cegłowska M., Dalay M.C. A new network for the advancement of marine biotechnology in Europe and beyond // Front. Mar. Sci. 2020. Vol. 7. Art. 278. https://doi.org/10.3389/fmars.2020.00278.

4. Haque N., Parveen S., Tang T., Wei J., Huang Z. Marine natural products in clinical use // Mar. Drugs. 2022. Vol. 20, N. 8. Art. 528 [1–40].

5. Donia M., Hamann M.T. Marine natural products and their potential applications as anti-infective agents // Lancet Infect. Diseas. 2003. Vol. 3, N. 6. P. 338–348.

6. Jeong S.H., Kim H.K., Song I.S., Lee S.J., Ko K.S., Rhee B.D., Kim N., Mishchenko N.P., Fedoryev S.A., Stonik, V.A., Han J. Echinochrome A protects mitochondrial function in cardiomyocytes against cardiotoxic drugs // Mar. Drugs. 2014. Vol. 12, N. 5. P. 2922–2936.

7. Jeong S.H., Kim H.K., Song I.S., Noh S.J., Marquez J., Ko K.S., Rhee B.D., Kim N., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome a increases mitochondrial mass and function by modulating mitochondrial biogenesis regulatory genes // Mar. Drugs. 2014. Vol. 12, N. 8. P. 4602–4615.

8. Lee S.R., Pronto J.R., Sarankhuu B.E., Ko K.S., Rhee B.D., Kim N., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Acetylcholinesterase inhibitory activity of pigment echinochrome A from sea urchin Scaphechinus mirabilis // Mar. Drugs. 2014. Vol. 12, N. 6. P. 3560–3573.

9. Kim H.K., Youm J.B., Jeong S.H., Lee S.R., Song I.S., Ko T.H., Pronto J.R., Ko K.S., Rhee B.D., Kim N., Nilius B., Mischchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome A regulates phosphorylation of phospholamban Ser16 and Thr17 suppressing cardiac SERCA2A $Ca^{2+}$ reuptake // Pflugers Arch. 2015. Vol. 467, N. 10. P. 2151–2163.

10. Shubina L.K., Makarieva T.N., Yashunsky D.V., Nifantiev N.E., Denisenko V.A., Dmitrenok, P.S., Dyshlovoy S.A., Fedorov S.N., Krasokhin V.B., Jeong S.H., Han J., Stonik V.A. Pyridine nucleosides neopetrosides A and B from a marine Neopetrosia sp. sponge. Synthesis of neopetroside A and its β-riboside fnalogue // J. Nat. Prod. 2015. Vol. 78, N. 6. P. 1383–1389.

11. Seo D.Y., McGregor R.A., Noh S.J., Choi S.J., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome A improves exercise capacity during short-term endurance training in rats // Mar. Drugs. 2015. Vol. 13, N. 9. P. 5722–5731.

12. Yoon C.S., Kim H.K., Mishchenko N.P., Vasileva E.A., Fedoreyev, S.A., Stonik V.A., Han J. Spinochrome D attenuates doxorubicin-induced cardiomyocyte death via improving glutathione metabolism and attenuating oxidative stress // Mar. Drugs. 2018. Vol. 17, N. 1. Art. 2 [1–20].

13. Kim H.K., Cho S.W., Heo H.J., Jeong S.H., Kim M., Ko K.S., Rhee B.D., Mishchenko N.P., Vasileva E.A., Fedoreyev S.A., Stonik V.A., Han J. A novel atypical PKC-Iota inhibitor, echinochrome A, enhances cardiomyocyte differentiation from mouse embryonic stem cells // Mar. Drugs. 2018. Vol. 16, No. 6. Art. 192 [1–14].

14. Yoon C.S., Kim H.K., Mishchenko N.P., Vasileva E.A., Fedoreyev S.A., Shestak O.P., Balaneva N.N., Novikov V.L., Stonik V.A., Han J. The protective effects of echinochrome A structural analogs against oxiative stress and doxorubicin in AC16 cardiomyocytes // Mol. Cell. Toxicol. 2019. Vol. 15. P. 407–414.

15. Park J.H., Lee N.K., Lim H.J., Mazumder S., Rethineswaran K.V., Kim Y.J., Jang, W. B.; Ji S.T., Kang S., Kim D.Y., Van L.T.H., Giang L.T.T., Kim D.H., Ha J.S., Yun J., Kim H., Han J., Mishchenko N.P., Fedoreyev S.A., Vasileva E.A., Kwon S.M., Baek S.H. Therapeutic cell protective role of histochrome under oxidative stress in human cardiac progenitor cells // Mar. Drugs. 2019. Vol. 17, N. 6. Art. 368 [1–15].

16. Kim R., Hur D., Kim H.K., Han J., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Chang W. Echinochrome A attenuates cerebral ischemic injury through regulation of cell survival after middle cerebral artery occlusion in rat // Mar. Drugs. 2019. Vol. 17, N. 9. Art. 501 [1–8].

17. Oh S.J., Seo Y., Ahn J.S., Shin Y.Y., Yang J.W., Kim H.K., Han J., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.S. Echinochrome A reduces colitis in mice and induces in vitro generation of regulatory immune cells // Mar. Drugs. 2019. Vol. 17. N. 11. Art. 622 [1–10].

18. Park G.B., Kim M.J., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J., Lee H.S., Kim D., Jeong J.Y. Echinochrome A promotes ex vivo expansion of peripheral blood-derived CD34(+) cells, potentially through downregulation of ROS production and activation of the Src-Lyn-p110δ pathway // Mar. Drugs. 2019. Vol. 17, N. 9. Art. 526 [1–14].

19. Kim J.M., Kim J.H., Shin S.C., Park G.C., Kim H.S., Kim K., Kim H.K., Han J., Mishchenko N.P., Vasileva E.A., Fedoreyev S.A., Stonik V.A., Lee B.J. The protective effect of echinochrome A on extracellular matrix of vocal folds in ovariectomized rats // Mar. Drugs. 2020. Vol. 18, N. 2. Art. 77 [1–15].

20. Yun H.R., Ahn S.W., Seol B., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J., Ko K.S., Rhee B.D., Seol J.E., Kim H.K. Echinochrome A treatment alleviates atopic dermatitis-like skin lesions in NC/Nga mice via IL-4 and IL-13 suppression // Mar. Drugs. 2021. V. 19, N. 11 Art. 622 [1–11].

21. Seol J.E., Ahn S.W., Seol B., Yun H.R., Park N., Kim H.K., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Han J. Echinochrome A protects against ultraviolet B-induced photoaging by lowering collagen degradation and inflammatory cell infiltration in hairless mice // Mar. Drugs. 2021. Vol. 19, N. 10. Art. 550 [1–13].

22. Park G.T., Yoon J.W., Yoo S.B., Song Y.C., Song P., Kim H.K., Han J., Bae S.J., Ha K.T., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim M.B., Kim J.H. Echinochrome A treatment alleviates fibrosis and inflammation in bleomycin-induced scleroderma // Mar. Drugs. 2021. Vol. 19, N. 5. Art. 237 [1–11].

23. Kim H.K., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Han J., Multifaceted clinical effects of echinochrome // Mar. Drugs. 2021. Vol. 19, N. 8. Art. 412 [1–16].

24. Song B.W., Kim S., Kim R., Jeong S., Moon H., Kim H., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Lee M.Y., Kim J., Kim H.K., Han J., Chang W. Regulation of inflammation-mediated endothelial to mesenchymal transition with echinochrome A for improving myocardial dysfunction // Mar. Drugs. 2022. Vol. 20, N. 12. Art. 756 [1–17].

25. Choi M.R., Lee H., Kim H.K., Han J., Seol J.E., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Ju W.S., Kim D.J., Lee S.R., Echinochrome A inhibits melanogenesis in B16F10 cells by downregulating CREB signaling // Mar. Drugs. 2022. Vol. 20, N. 9. Art. 555 [1–12].

26. Ahn J.S., Shin Y.Y., Oh S.J., Song M.H., Kang M.J., Park S.Y., Nguyen P.T., Nguyen, D. K., Kim H.K., Han J., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Seo Y., Lee B.C., Kim H.S. Implication of echinochrome A in the plasticity and damage of intestinal epithelium // Mar Drugs. 2022, No. 20, N. 11. Art. 715 [1–14].

27. Kim J.M., Shin S.C., Cheon Y.I., Kim H.S., Park G.C., Kim H.K., Han J., Seol J.E., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Lee B.J., Effect of echinochrome A on submandibular gland dysfunction in ovariectomized rats // Mar. Drugs. 2022. Vol. 20, N. 12. Art. 729 [1–14].

28. Tang X., Nishimura A., Ariyoshi K., Nishiyama K., Kato Y., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.K., Han J., Kanda Y., Umezawa K., Urano Y., Akaike T., Nishida M. Echinochrome prevents sulfide catabolism-associated chronic heart failure after myocardial infarction in mice // Mar. Drugs. 2023. Vol. 21, N. 1. Art. 52 [1–17].

29. Han D.G., Kwak J., Choi E., Seo S.W., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.K., Han J., Byun J.H., Jung I.H., Yun H., Yoon I.S. Physicochemical characterization and phase II metabolic profiling of echinochrome A, a bioactive constituent from sea urchin, and its

physiologically based pharmacokinetic modeling in rats and humans // Biomed. Pharmacother. 2023. Vol. 162. Art. 114589 [1–16].

30. Kim S.E., Chung E.D.S., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Kim H.K., Nam J.H., Kim S.J. Multiple effects of echinochrome A on selected ion channels implicated in skin physiology // Mar. Drugs. 2023. Vol. 21, No. 2. Art. 78 [1–16]

31. Pham T.K., Nguyen T.H.T., Yun H.R., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Vu T.T., Nguyen H.Q., Cho S.W., Kim H.K., Han J. Echinochrome A prevents diabetic nephropathy by inhibiting the PKC-iota pathway and enhancing renal mitochondrial function in db/db mice // Mar. Drugs. 2023. Vol. 21, N. 4. Art. 222 [1–15].

32. Jin J.O., Shastina V.V., Shin S.W., Xu Q., Park J.I., Rasskazov V.A., Avilov S.A., Fedorov, S.N., Stonik V.A., Kwak J.Y., Differential effects of triterpene glycosides, frondoside A and cucumarioside A2-2 isolated from sea cucumbers on caspase activation and apoptosis of human leukemia cells // FEBS Lett. 2009. Vol. 583, N. 4. P. 697–702.

33. Park J.I., Bae H.R., Kim C.G., Stonik V.A., Kwak J.Y., Relationships between chemical structures and functions of triterpene glycosides isolated from sea cucumbers // Front. Chem. 2014. Vol. 2. Art. 77 [1–14].

34. Yun S.H., Park E.S., Shin, S.W., Na Y.W., Han J.Y., Jeong J.S., Shastina V.V., Stonik V.A., Park J.I., Kwak J.Y. Stichoposide C induces apoptosis through the generation of ceramide in leukemia and colorectal cancer cells and shows in vivo antitumor activity // Clin. Cancer Res. 2012. Vol. 18, N. 21. P. 5934–5948.

35. Yun S.H., Park E.S., Shin S.W., Ju M.H.; Han, J.Y., Jeong J.S., Kim S.H., Stonik V.A., Kwak J.Y., Park J.I. By activating Fas/ceramide synthase 6/p38 kinase in lipid rafts, stichoposide D inhibits growth of leukemia xenografts // Oncotarget. 2015. Vol. 6, N. 29. P. 27596–27612.

36. Yun S.H., Sim E.H., Han S.H., Kim T.R., Ju M.H., Han J.Y., Jeong J.S., Kim S.H., Silchenko A.S., Stonik V.A., Park J.I. In vitro and in vivo anti-leukemic effects of cladoloside C2 are mediated by activation of Fas/ceramide synthase 6/p38 kinase/c-Jun NH2-terminal kinase/caspase-8 // Oncotarget. 2018 Vol. 9, N. 1. P. 495–511.

37. Cui H., Liu J., Vasileva E.A., Mishchenko N.P., Fedoreyev S.A., Stonik V.A., Zhang, Y., Echinochrome A reverses kidney abnormality and reduces blood pressure in a rat model of preeclampsia // Mar. Drugs. 2022. Vol. 20, N. 11. Art. 722 [1–13].

38. Daniotti S., Re I. Marine biotechnology: challenges and development market trends for the enhancement of biotic resources in industrial pharmaceutical and food applications. A statistical analysis of scientific literature and business models // Mar. Drugs. 2021. Vol. 19. N. 2. Art. 61 [1–35].

39. Lindequist U. Marine-derived pharmaceuticals–challenges and opportunities // Biomol. Ther. 2016. Vol. 24, N. 6. 561–571.

40. OECD, Marine Biotechnology and the Bioeconomy. Paris: OECD, 2012.