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COLLAGENASES IN MEDICAL PRACTICE: MODERN COLLAGENASE-BASED PREPARATIONS AND PROSPECTS FOR THEIR IMPROVEMENT

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The aim of this study was to assess the coverage of studies of collagenolytic enzymes (collagenases) in the sphere of their use in wounds and scars treatment, the resource of their production and the range of collagenase products to identify the areas for their improvement.

Materials and methods. The information from retrieval and library databases (eLIBRARY, PubMed, Scopus, ScholarGoogle, ResearchGate), patent information databases (freepatent.ru, ntpo.com, fips.ru), the State register of medicines (GRLS) and the State register of medical devices, as well as technical information provided by manufacturers of medicines and medical devices, was used in the article.

Results. The analysis of the information database has shown that collagenolytic enzymes are effective proteolytic complexes because of their ability to provide the breakdown of collagen, the main component of wounds and scars.

Hepatopancreas crustaceans is currently one of the available raw resources of collagenases in Russia. It is noted that proteolytic enzymes from the Paralithodes camtschatica hepatopancreas are characterized by a broad specificity: they are able to hydrolyze both native collagen and other protein substrates. There are data confirming the capability of collagenases to accelerate the process of reparation in addition to wound cleansing from a necrosis. The results of clinical studies of collagenases anti-scar properties, indicate the effectiveness of their use for the skin scar correction. The content analysis has shown that there is a small amount of collagenase-based products in the Russian pharmaceutical market: lyophilized powder for preparation of the injection solution “Collalysin”, recommended for scars treatment; a medical dressing “Digestol” with collagenase, recommended for wounds and necrotic lesions treatment; “Fermencol” (gel and powder), the “Karipain plus” gel for scars treatment. Drugs are represented by only powder lyophilisate “Collalysin”.

Conclusion. The development of gel compositions (Aerosil-based oleogels) and atraumatic dressings with collagenase from Paralithodes camtschatica hepatopancreas as the most affordable raw materials can be considered problem number one of practical pharmacy at present. This provides for the creation of the dosage forms, improved in terms of stability and efficiency, as well as ease of use.

Keywords: collagenolytic enzymes, Paralithodes camtschatica collagenase, scars, wounds, preparations, gels

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КОЛЛАГЕНАЗЫ В МЕДИЦИНСКОЙ ПРАКТИКЕ: СОВРЕМЕННЫЕ СРЕДСТВА НА ОСНОВЕ КОЛЛАГЕНАЗЫ И ПЕРСПЕКТИВЫ ИХ СОВЕРШЕНСТВОВАНИЯ

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Цель. Оценка состояния изученности применения коллагенолитических ферментов (коллагеназ) в терапии ран и рубцов, источников их получения, ассортимента средств с коллагеназой для выявления направлений их совершенствования.

Материалы и методы. В работе использованы информационно-поисковые и библиотечные базы данных (eLIBRARY, PubMed, Scopus, ScholarGoogle, ResearchGate), патентно-информационные базы (freepatent.ru, ntpo.com, fips.ru), Государственный реестр лекарственных средств и Государственный реестр медицинских изделий, а также техническая информация, представленная производителями лекарственных средств и медицинских изделий.

Результаты. Анализ информационных источников показал, что коллагенолитические ферменты являются эффективными протеолитическими комплексами, т.к. обладают способностью обеспечивать расщепление коллагена, являющегося главным компонентом ран и рубцов. Одним из доступных сырьевых источников коллагеназ в России в настоящее является гепатопанкреас ракоообразных. Отмечается, что для протеолитических ферментов из гепатопанкреаса камчатского краба характерна широкая специфичность: они способны гидролизовать как нативный коллаген, так и другие белковые субстраты. Имеются данные исследований, подтверждающие, что коллагеназы наряду с очисткой раны от некроза способны ускорять процесс ее репарации. Результаты клинических исследований противорубцовых свойств коллагеназ свидетельствуют об эффективности их использования для коррекции рубцовых изменений кожи. Контент-анализ показал, что на российском фармацевтическом рынке присутствует незначительное количество средств на основе коллагеназ – лиофилизированный порошок для приготовления раствора для инъекций («Коллализин»), рекомендуемый для лечения рубцов; медицинская повязка с коллагеназой, рекомендуемые для лечения ран и некротических поражений «Дигестол»; гель и порошок «Ферменкол», гель «Карипаин плюс» для лечения рубцов. Лекарственные препараты представлены только порошком-лиофилизатом «Коллализин».

Заключение. Разработка состава гелей (олеогелей на основе аэросила) и атравматических салфеток с коллагеназой из гепатопанкреаса краба как наиболее доступного сырья можно считать актуальной задачей практической фармации. Это предусматривает создание лекарственных форм, улучшенных с позиций стабильности и эффективности, а также удобства использования.

Ключевые слова: коллагенолитические ферменты, коллагенза камчатского краба, рубцы, раны, препараты, гели

INTRODUCTION

The problem of effective and rapid healing of wounds resulting from injuries of different origins, remains one of the most relevant in modern medical practice. Currently, the effectiveness of wound healing is determined not only by the term, but also by the aesthetic result achieved. In addition, special attention is paid to the treatment convenience to combine the optimal therapeutic effect and a patient's life quality [1].

In medical practice, preparations of proteolytic enzymes are used to accelerate the granulation process and reduce the time of wound healing by the ability to cleanse wounds from necrotic tissues and exudate. Preparations of proteolytic enzymes (collagenase, hyaluronidase) are also used for scars medical correction [2, 3].

The use of enzyme preparations in the composition of external therapy, has some peculiarities caused mainly by their instability, which makes it relevant to improve the existing dosage forms both in terms of stability and efficiency, and ease of use. Collagenases are one of the most effective proteolytic enzymes due to their ability to provide collagen, the main component of wounds and scars. Thus, studuing the problems related

to collagenolytic enzymes raw resources, mechanisms of their action, clinical efficacy of collagenases in wounds and scars, as well as the range and features of the use of collagenase-based products in medical practice, are relevant.

THE AIM of the review is to assess the research of collagenolytic enzymes (collagenases) use in the treatment of wounds and scars, the sources of their production, the range of collagenase products to identify the areas for their improvement.

MATERIALS AND METHODS

The information from retrieval and library databases (eLIBRARY, PubMed, Scopus, ScholarGoogle, ResearchGate for the time interval from 2000 to 2019), patent information databases (freepatent.ru, ntpo.com, fips.ru), reference literature, the State Register of Medicinal Remedies (SRMR) and the State Register of Medical Products, (SRMP) as well as technical information provided by manufacturers of medicines and medical products, the sites dedicated to cosmetic products "Fermencol" and "Karipain", is used in the article. The depth of the patent search was 30 years. The keywords in the search process are: collagenase, collagenolytic enzymes, enzyme immobilization, wounds, treatment, scars.

RESULTS AND DISCUSSION

The role of enzyme preparations in the correction of pathological wound healing

Wound healing is a complex biological process that consists of overlapping phases: inflammation, proliferation, and remodeling. Wound healing is a regulated process in which several cell types (keratinocytes, fibroblasts, endothelial cells, macrophages and platelets) and a network of signaling molecules (cytokines, chemokines and growth factors) are in effect. In its course, the disorders which can lead to hard-to-heal chronic wounds or scars are possible. The most common factors impeding normal healing are diabetes, venous disease, old age, peripheral neuropathy, impaired microflora and malnutrition. A wound is considered chronic when it does not show a tendency to repair for more than 4 weeks. So, according to the data, full and complete wound closure, is achieved in only 25-50% of cases of chronic or hard-to-heal wounds after 20 weeks' treatment, especially in the case of venous and diabetic ulcers. Chronic hard-to-heal wounds are often characterized by a number of microbiological (increased microbial contamination, including the presence of biofilms), biochemical and cellular pathologies that prevent or slow down the process of healing. Unlike acute wounds, chronic wounds are not completed by the process of remodeling, but are considered as a process stopped at the stage of inflammation or proliferation [1–4].

The presence of cellular detritus, necrotic tissues and bacterial toxins leads to the prolongation of inflammation and increased production of cytokines by macrophages and neutrophils, resulting in the activation of macrophages and fibroblasts. An excessive activity of tissue proteases is observed [3].

The so-called "wound bed preparation" technology is used to remove the necrotic component to transfer the wound from a chronic state to an acute one. Traditionally, to remove necrotic, damaged or infected tissues, different methods are used: surgical, autolytic, enzymatic, chemical and physical. Wound cleansing helps to reduce the presence of inflammatory cytokines and metalloproteinases, which are produced during chronic wounds inflammation [4].

One of the problems of pathological wound healing is the scars (keloid and hypertrophic) formation, which occurs when the regulation by fibroblasts and keratinocytes balance of collagen synthesis-breakdown process disrupts, and the disturbance of the collagen remodeling process takes place. A stimulating effect on fibroblasts is provided by a chronic inflammation of the scar tissue, a long-term wound healing, secondary infections and epithelialization disruption [1].

Enzymatic wound cleansing is an effective and selective method, often used in combination with other methods of treatment, e.g., in combination with moisturizing dressings. In chronic wounds, it is necessary not only for cleansing (removal of necrotic tissue), but also for the migration of cells involved in epithelialization, as well as the elimination of inflammation. Unlike acid preparations used for treatment of wounds with a high content of necrotic tissues, e.g., the ointment containing salicylic acid 40%, proteases have no effect on intact tissues [2, 3].

Collagen is the most stabile protein of tissue detritus. In this case, the wounds containing collagen fibers, hardly give way to enzymatic cleansing by means of other proteolytic enzymes: trypsin, chymopsin, papain, terrilitin, streptokinase, etc. [2]. Collagenase preparations are successfully used to treat wounds with massive purulonecrotic discharge, trophic ulcers, frostbite, burns, scars. Proteolytic enzymes with collagenolytic activity are the most effective for the wounds' treatment and elimination of scarring [5–11].

Characteristics of collagenases used in medical practice: sources of production, mechanism of action, data of pharmacological and clinical studies

Collagenase is a specific proteolytic enzyme that breaks down peptide bonds in natural collagen, the main structural element of a connective tissue. According to the active ingredient resource, collagenase preparations are biological agents, because their industrial raw materials are microorganisms' cultures or animals' digestive glands.

The analysis of the commercial drugs, veterinary and medical products, cosmetics composition with collagenases showed, that modern products contain enzyme

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complexes, the source of which are the Clostridium family bacteria or digestive tract glands (hepatopancreas) of the *Paralithodes camtschaticus* [12–15].

Collagenases derived from Clostridium histolyticum, the most commonly used drug-derived microbial proteases, are single-stranded proteins with masses ranging from 68 kDa to 130 kDa. Thus, the "Santil" ointment contains two collagenases (collagenase G, ~114 kDa, and collagenase H, ~110 kDa), nonspecific neutral metalloproteinase (~35 kDa), a small amount of cysteine proteases (clostripain ~58 kDa). The disadvantages of microbial collagenase preparations are: a relatively low activity, difficulties in cultivating producers, as well as potential allergenicity, which may be caused by the usage of pathogenic microorganisms-producers [4, 11, 12].

In Russia, hepatopancreas *Paralithodes* of crustaceans is widely used as a source of collagenase, which is considered as an affordable, cheap and non-toxic raw material, being a waste of commercial crab processing. The research of this group of proteases is devoted to both the production of stable and highly active enzyme complexes and the development of effective drugs [13–19].

Hepatopancreas crustaceans produces a number of digestive enzymes that hydrolyze different classes of biopolymers: collagenolytic (serine, trypsin-like) proteases, collagenases, phosphotases, phosphodiesterases, elastases, RNAses, DNAses, etc. It has been proved that proteolytic enzymes of *Paralithodes camtschaticus,* possess a broad specificity. They disintegrate both native collagen and other protein substrates – casein, gelatin, fibrinogen and serum albumin, which, in many respects, leads to the high efficiency of these complexes [14, 16, 20]. The enzyme complexes obtained from the *Paralithodes camtschaticus* hepatopancreas, vary according to the degree of purity, activity and composition. Thus, the sum of collagenolytic proteases of crab hepatopancreas, which is a mixture of nine proteins with a molecular weight of 23–36 kDa, was isolated. In the preparations "Collalitin" and "Collagenase KK", collagenolytic proteases of *Paralithodes camtschaticus* hepatopancreas are represented in the form of three isoenzymes, the molecular weight of which is in the range from 18 to 27 kDa [12, 15–20].

The mechanism of a therapeutic action of collagenases is based on the ability to convert native insoluble collagen into a soluble form by hydrolysis of peptide bonds. True collagenases, particularly of microbial and animal origin (the metalloproteases class), cleave the triple helix of collagen at one specific point, forming large soluble fragments, further destruction of which is relatively slow. It has been established that purified clostridial collagenase, as well as the complex of enzymes present in the "Santil" preparation, hydrolyze native and denatured collagen, as well as collagen-associated proteins of the intercellular matrix to peptides. Serine proteases (collagenolytic proteases) obtained from the gastrointestinal tract of fishes and invertebrates, break down the three polypeptide chains of tropocollagen, and the resulting peptides are further hydrolyzed to amino acids [2, 11, 12, 20–26].

It is noted that in the wound, proteolytic enzymes contribute to the exudate colliquation, facilitating the access for antiseptic and antibiotic drugs to the bacterial cell, enhancing the effect of antibacterial therapy. On the model of an infected rats' burn it was established that the collagenase tretment of the wound formation from day 5 from the beginning of the process reduced a bacterial load from 108 to 105 or fewer bacteria per gram of tissue. The level of bacterial load had a beneficial effect on normal wound healing, which contributed to the reparation acceleration. The authors suggest that collagenases can be safely used without concomitant local antimicrobials in chronically infected wounds due to their antimicrobial properties and effectiveness of wound healing [25, 26].

In the studies it has been established, that in addition to cleansing the wound of necrotic tissues, collagenases directly affect the reparation process. Thus, collagenase isolated from *C. histolyticum,* was found to enhance migration and proliferation of keratinocytes, endothelial cells and fibroblasts. The study of the effect of bacterial collagenase preparations on the model of full-layer wound in Yucatan pigs showed, that the daily treatment with the enzyme from the first day of the wound formation, made it possible to achieve purification, exudation, as well as effective angiogenesis and epithelization and, as a result, effective wound healing in a shorter time [28].

The reparative effect of proteolytic complexes obtained from crustaceans, has also been revealed. The study of moricrasa (a lipophilic base ointment with *Paralithodes camtschaticus* collagenase) reparative properties on the spontaneous purulent-ulcer injuries in rats, showed a complete wound healing after 6–10 days, when applied daily. It has also been noted that the further application of the ointment, contributed to the resumption of the wool cover at the wound location [29].

The study of reparative properties of oleogel with *Paralithodes camtschaticus* collagenase on the rats' burn skin model showed, that the test ointment, applied every day beginning from the 3rd day after the infection and formation of spontaneous purulent-necrotic wounds, activated the processes of epithelization and proliferation in the damaged tissues, which significantly reduced the healing time – there was complete epithelization of the burn surface, desquamation of the scab on the 10th day, in comparison with the control group, where incomplete epithelization was observed [30].

In the experiments on the animals (rats) it was demonstrated, that the wounds treatment with chitosan-modified textile with immobilized collagenase of *Paralithodes camtschaticus,* significantly reduced the necrotic tissue to 3 days (14 days in the control) and the

purulent wounds healing time reduced to 12 days (27 days in the control) [18].

Attempts to research the mechanism of microbial collagenases influence on the wound healing effectiveness were carried out. *In vitro* research has established, that the intercellular matrix enzymolysis with bacterial collagenase and the "Santil" ointment, containing collagenases, releases peptides that activate cellular migration, proliferative and angiogenic processes in trauma and promote wound healing. *In vitro* research has also revealed that collagen hydrolysis fragments and collagen-associated peptides obtained as a result of endothelial collagenase hydrolysis of dermal capillaries and human fibroblasts, increase cell proliferation and promote angiogenesis. On the model of full-layer long-term non-healing wounds of the mice, it was demonstrated that collagenase of "Santil" ointment, as well as peptides obtained from extracellular matrix, increase wound reepithelization by 60–100% compared to the control (saline solution) during the daily treatment, starting from the first day of damage [10].

The effect of the "Santil" ointment on the resolution of inflammation in long-term unhealed wounding was investigated. The research was carried out on macrophages, isolated from wounds treated with ointment or petrolatum (a comparison drug), and implanted in mice. A significant increase in pro-reparative and a decrease in pro-inflammatory macrophages polarization in both acute inflammatory process and chronic diabetic wound, have been revealed. Wound macrophages in the ointment-treated group showed an increased production of anti-inflammatory cytokines IL-10 and TGF-β, as well as a reduced production of pro-inflammatory cytokines TNF-α and IL-1β. Wound treatment with clostridial collagenase attenuated the transactivation of factor NF-KB and significantly reduced STAT6-phosphorylation. These results, make it possible to consider collagenase as a potential anti-inflammatory agent that can be effective in chronic wound inflammation, including diabetic wounds [31]. There are numerous data on the effectiveness of the "Santil" ointment, used as a wound healing agent in clinical practice. The data confirm that the ointment based on collagenase, is safe and effective for the treatment of skin ulcers and burn wounds, helping to reduce the healing time and the severity of pain symptoms, reduce the risk of infection. The effectiveness of the "Santil" ointment for surgical treatment of diabetic foot ulcers, bedsores and trophic varicose ulcers, as well as burns, has been demonstrated in a number of clinical trials in various institutions (for example, inpatient, outpatient and long-term kinds of care) [32–34].

The data of clinical studies of the "Moricrol" ointment containing *Paralithodes camtschaticus* collagenase, were registed. The use of the ointment in patients with hard-to-heal skin wounds and the wounds after skin transplantation, contributed to the engraftment of transplants in patients and the absence of rough deforming scars. A reduction of the healing time of extensive wounds in the mucosa of the oral cavity when using the "Moricrol" ointment, was revealed. It has been noted that the treatment with "Moricrol" in purulent wounds, contributed to a faster wound surface cleansing [35].

In clinical research it was found out, that the combined application of wound coating "Multiferm" (the collagenase *Paralithodes camtschaticus* and chitosan complex), photodynamic and NO-therapy, accelerated the defect reparation in the case of trophic ulcers. It was manifested in accelerate purifying of purulent necrotic content от гнойно-некротического содержимого and the granulation formation 2.4 times faster. The average healing time also decreased by an average of 9.2 days [36].

Clinical efficacy of various collagenase-based anti-scar agents has been studied. The effectiveness of collagenases in the scar therapy is associated with their ability to hydrolyze collagen excess [37–41]. For example, the possibility of hypertrophic scars correction by means of electrophoresis in a solution of weak electrolytes with the "Polycollagenase-K" preparation has been investigated. During the treatment, the analysis of the scars state was carried out by EHF-dielectrometry method. The tendency of the moisture content increase in the scar tissue has been revealed. It was associated with an increase in the fraction of intracellular structured water. It has been detected that the hydration of the scar tissue under the influence of "Polycollagenase-K", approached the values peculiar to those of healthy skin at the similar localization. According to the authors' data, the increase in the moisture content in the scar tissues, was due to the water release during the collagen hydrolysis. Alongside with the destruction of the excess collagen, the normalization of microcirculation was noted [8, 39].

The anti-scar activity of the collagenolytic complex from sea stars has been proved: the ability to influence the reduction of collagen gel, the activity of matrix metalloproteinases (MMP), the release of hydroxyproline and the regulation of the activity of fibroblast genes. It was found out, that the complex significantly inhibited the reduction of collagen gel after 2 days of incubation. The expressed activity of MMP-2 and MMP-9 was revealed, which was manifested in the form of a large amount of hydroxyproline release. The fibroblast cell culture treatment significantly reduced fibrocyte proliferation in 3-day cultures. The ability to influence the expression of genes controlling the inflammatory response in fibroblasts, has been established [42].

The clinical studies of the anti-scar properties of the "Moricrol" ointment, detected a decrease in the manifestations of redness, itching and a sense of tightening of keloid scars. In 46 patients, a significant improvement in the condition of the skin, namely paling of tissues and some flattening of the scar tissue in the scar area was revealed. Some softening of the scar and a decrease in the turgor of the scar skin on palpation. was assessed How-

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ever, in some patients (18 patients), no tissue softening occurred, and in 5 patients with chronic burn scars, the expected effect was absent [35].

There are research data on gel (group 1 – applications and group 2 – phonophoresis) and a solution (group 3 – electrophoresis) for scars correction with "Fermencol" containing *Paralithodes camtschaticus* collagenase in patients with hypertrophic and keloid scars of different origins. A statistically significant slowdown in the scar growth, paresthesia and itching reducing, scar thickness reducing, the disappearance of inflammation signs was detected when using the gel and solution "Fermencol" after the treatment course of 10-15 days. It was revealed that the use of therapeutic electrophoresis and ultrasound with "Fermencol"®, made it possible to significantly increase the drug intake into the skin [41].

The influence of electro- and ultraphonophoresis "Fermencol" on clinical manifestations of pathological scars in 89 patients with hypertrophic and keloid skin scars, has been investigated. The scars treatment with "Fermencol" electro-and ultraphonophoresis, contributed to a more significant dynamics of clinical signs, compared with "Contractubex" and "Lidase" electro – and ultraphonophoreses. The maximum reduction in clinical manifestations – type, consistency, color and sensitivity of the scar – was observed under the "Fermencol" ultraphonophoresis. The defibrosing effect was most evident with the combination of the drug and the ultrasound exposure [43].

A new method of treatment and prevention of hypertrophic and keloid scars, which implies lidase injection into the thickness of the scar tissue, followed by wet coating containing chitosan and collagenase application to the scars surface in the course of 10-15 procedures, has been developed, patented and clinically tested.

This method's clinical approbation showed a significant improvement in both – the clinical picture and the patient's life quality – in relation to the comparison course (collagenase was administered transdermally in therapeutic doses, and lidase was administered intradermally by the course of 10-15 daily procedures) [44].

The method of skin scars after the acne correction by means of a course treatment with the "Fermencol" electrophoresis. In group 1, applications of the «Fermencol» gel were used twice a day, in the 2nd group, electrophoresis of the fermencol solution was carried out. A positive result in 86.4% of patients of group 1 and 94.1% of patients of group 2 was revealed: slowing down of the active growth, regression of the scar, disappearance of unpleasant subjective sensations, alignment of the color of the scar and surrounding tissues [45].

In clinical studies, the evaluation of the treatment of hypertrophic scars on patients after surgical interventions on the thyroid gland. The treatment was carried out by collagenase in the form of the dry "Collalysin" powder (collagenase Clostridium histolyticum), mixed up with petrolatum. The positive effect, was observed in a month from the beginning of the treatment by this drug. Collagenase treatment has shown the results similar to the administration of triamcinolone, a hormonal anti-inflammatory drug, into the scar [46]. An emulsion-based composition of "Collalysin" has also been developed for the prevention and treatment of hypertrophic and keloid scars resulting from burns, dermabrasion and plastic surgery [47].

Modern collagenase-based products: assortment in the Russian pharmaceutical market, opportunities for improvement

In the literature data, there is information about the developed and patented medicines based on collagenase. So, the "Collagenase KK" preparation was produced in the form of the lyophilized powder for the application to damaged tissues or aqueous solutions prepared ex tempore and used for wetting wipes or tampons [6, 17, 48]. The disadvantage of this form is the following: the activity of proteolytic enzymes, when directly introduced into the wound, lasts 15-30 minutes, making the therapy ineffective because of inactivating the enzymes. The process is as also characterized by a the relative complexity [49].

Some hydrophilic gels have been developed, e.g., a polyethylene oxide gel with collase [50, 51]. To include *Paralithodes camtschaticus* collagenase, a composition consisting of a mixture of vinylglutarate, vinyl acetate and vinyl alcohol, which turns into a gel-like state when interacting with the wound contents, was used by I. Yu. Sakharov et al. [24]. The ointments on lipophilic bases were offered. So, the ointment with collagenase from Clostridium histolyticum was based on petrolatum. The moricrase "Moricrol" ointment on the lipophilic basis of "Eikonal" (a mixture of fatty acids and vitamins A, E, D and F) is known [19]. Currently, these drugs are not available on the pharmaceutical market [6, 52].

The analysis of the literatyre data showed that currently, collagenase-based products are available for the preparation of solutions for injection and electrophoresis forms, ointments, creams and medical dressings, in the form of powders [4–8, 52–55].

The following commercial drugs are produced abroad: the "Iruksol" and "Santil" ointments produced by "Smith&Nephew". They include collagenase C. histolyticum as a proteolytic complex. It should be noted that these drugs are not registered in the Russian pharmaceutical market [10, 52].

General Residual Life of the System (GRLS) – Encyclopedia of drugs – presents information about the "Collalysin" drug (the INN "Collagenase"), LSR-005615/09 is a proteolytic agent, an enzyme preparation obtained from the culture of C. histolyticum. "Collalysin" has a keloidolytics effect**.** It is available in the form of a powder-lyophilizate dosage form and strength from 100 КЕ to 1000 КЕ for a solution for injections and electrophoresis preparation and is recommended for treatment of burns, correction of scars, etc. [6, 52].

"Fermencol" (Russia) is a cosmetic product based on the enzymes of collagenase hydrobionts, designed for the correction of scars. It is available in the form of gel and a set for preparing an electrophoresis solution [54, 55].

A self-absorbable biological dressing "Digestol", Russia) is a wound set (RCF 2008/02946). It contains the sum of collagenolytic trypsin-like proteases (collagenases) of *Paralithodes camtschaticus*. It is recommended for the use in purulent and infected wounds, bedsores, trophic ulcers, burns, a diabetic foot syndrome. Dissolving in the wound contents, the wound coating releases the enzyme in the active form. A necrolytic effect of the wound dressing is combined with an anti-inflammatory and regeneration activating effect due to the presence of collagen [8].

Collagenase is also included in the cosmetic product – a dry "Karipain Plus" balm, containing a complex of enzymes: papain, bromelain and collagenase, intended for the treatment of scars [56].

Thus, the Russian pharmaceutical market currently has a small number of collagenase-based products: a lyophilized powder for the preparation of an injection solution ("Collalysin"), recommended for the scars treatment; a medical dressing with collagenase, recommended for the treatment of wounds and necrotic tissues "Digestol"); cosmetic gel and powder "Fermencol", a dry balm "Karipain Plus", recommended for the scars treatment. The drugs are represented by only powder-lyophilizate for the preparation of injection solutions and electrophoresis.

A pharmaceutical development of external drugs with proteolytic enzymes, in addition to justifying the optimal dosage form, makes provision for an ointment base or carrier, that ensure the enzyme stability. The analysis of the scientific and technical literature database as well as patents showed the following methods used: enzyme stabilization, the use of lipophilic base, immobilization on a polymer carrier [16, 24, 57, 58].

So, to preserve the activity of the enzyme in the drug, it is possible to use stabilizers, for example, salts. In particular, ammonium sulfate in a certain concentration reversibly inactivates proteolytic enzymes by precipitation, preventing their autolysis. Sulfate ions interact with positively charged amino acids, giving the protein molecule a more compact shape, making it less soluble. This method of enzyme stabilization is implemented in the "Fermencol" gel [59].

In the ointments with collagenase from C. histolyticum, petrolatum is used ("Iruxol", "Santil"). Based on petroleum jelly and paraffin, the veterinary ointment "Iruxovetin" containing collagenase, was previously produced. The use of these bases is due to the fact that lipophilic components do not contain water, which is a medium for the enzymes autolysis and reproduction of microorganisms-destructors, which makes it possible to preserve the activity of enzymes for a long time [3, 4, 25].

But as a base, petroleum jelly is characterized by a number of drawbacks: an occlusive effect and a low osmotic activity, which, for a favorable repair, can negatively affect the wound state requiring oxygen and an exudate outflow..

The ointments based on petrolatum, cause inconvenience, i.e., they are poorly washed off with water, because of the pronounced viscosity they are distributed over the surface of the skin with effort. In this regard, the search for the bases devoid of these shortcomings, but at the same time ensuring the preservation of the enzyme activity during the storage period, can be considered a hot topic [5, 52].

Oleogels, e.g. based on Aerosil, can be considered promising bases for preparations of proteolytic enzymes. Thanks to the gel-like structure, gels are easily applied and distributed over the skin. An additional advantage of this base. can be considered the fact, that Aerosil exhibits a high sorption capacity against the decay products of tissues, toxins, microorganisms. The oleogel containing silicones, has also been proven to be effective as a scars treatment [60, 61].

Currently, in external medicines, immobilized enzymes are used on polymer carriers. Immobilization makes it possible to limit the activity of proteolytic enzymes by the damaged area and increases their stability in the wound environment. Thus, when using the enzymes immobilized on fiber-forming carriers, the terms of purification and wound healing are significantly reduced, the consumption of drugs is also reduced in comparison with the free enzymes use [62, 63].

Preparation of fibrous materials with proteolytic enzymes by covalent immobilization, providing activation of the fiber surface, in particular by treatment with oxidants to obtain dialdehyde cellulose, can serve an example, Active aldehyde groups interacting with functional groups of the enzyme to form covalent bonds, are formed on the fiber surface resulting in its fixation [63, 64].

For example, in the "Multiferm" dressing, a copolymer on the basis of dialdehydecellulose treated with chitosan with immobilized enzyme complex of *Paralithodes camtschaticus* hepatopancreas was used. However, one of the problems of chitosan-containing textile dressings, is the "keratinization" of the dressings edges, associated with structural changes in chitosan during immobilization, sterilization and storage. Currently, studies to obtain more stable preparations of immobilized enzymes with improved functional characteristics, are being conducted in this direction [7, 65].

One of the options for improving the properties of textile dressings, is conferring atraumatic characteristics provided by water-repellent impregnation, e.g., ointments or gel coatings. E.g., a hydrophobic ointment base (the "Branolid" dressing) or wax ("Voscopran") prevent sticking to the wound and traumatization of the granulations in the process of dressing changes. Changing such a dressing is painless for the patient [66].

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Based on this, the research on the creation of atraumatic wipes with immobilized collagenase on a hydrophobic basis can be considered perspective, in our opinion.

CONCLUSION

Collagenases are among the most effective proteolytic enzymes, because of their ability to provide the cleavage of collagen, the main component of wounds and scars. In addition, there are data from preclinical and clinical studies confirming, that collagenases of various origins, alongside with their necrolytic activity, are able to accelerate the process of reparation. Biochemical distinctions of collagenase influence on the wound healing process, as well as biochemical aspects of collagenase anti-inflammatory effect, have been investigated. The results of clinical studies of anti-scar properties of collagenases of different origins confirming their effectiveness in this pathology, have been registed. One of the available raw resources of collagenolytic enzymes is currently the hepatopancreas of crustaceans, in particular, *Paralithodes camtschaticus*. Due to the composition peculiarities, the enzymes derived from *Paralithodes camtschaticus* hepatopancreas, have a wide specificity as they hydrolyze both native collagen and other protein substrates (gelatin, casein, fibrinogen and serum albumin).

On the pharmaceutical market of the Russian Federation, the range of products with collagenase is not wide, so its expansion can be relevant. The collagenase derived from *Paralithodes camtschaticus* hepatopancreas, can be used as the most affordable raw material with pronounced collagenolytic properties. As the dosage form, more convenient in application and production, gels have their set of advantages**.** Thanks to their potential sorption properties, the oleogels based on aerosil, can be considered a promising base for external remedies with collagenolytic enzymes,. The development of gels and atraumatic dressings with collagenase obtained from *Paralithodes camtschaticus* as the most affordable raw materials, can be considered significant for practical pharmacy.

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All authors had equally contributed to the research work.

CONFLICTS OF INTEREST

The authors and peer reviewers of this paper report no conflicts of interest.

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