Scientifically Based Development of an Innovative Gauze Dressing with a Combined Composition for Accelerated Wound Healing

Hava Ali Kizi Karimova*, Mukhtar Dzheiranov, Maleika Elnurovna Garaeva, Turkan Kamandar Kizi Sharifova, Fizze Ruslanovna Zaidova, Kseniya Romanovna Korovko, Olga Vladimirovna Belyakova, Askar Satkalievich Chumbaev, Diana Magomedovna Madagova, Andrey Viktorovich Matyukhin

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Abstract

The development of effective and safe means for local wound treatment remains an urgent problem in modern medicine. The purpose of this study was to create an innovative drug in the form of an impregnated gauze bandage, ready for immediate use. The formulation is based on a synergistic combination of zinc sulfathiazole, which provides antimicrobial action and delivery of zinc ions as a regeneration cofactor, dexpanthenol, for direct stimulation of cell proliferation and epithelialization, and standardized tea tree essential oil, which has additional antiseptic and anti–anti-inflammatory activity. The paper presents a proven production technology that guarantees the stability of the

Hava Ali kizi Karimova*

Department of Dentistry, Institute of Dentistry, Saratov State Medical University named after V.I. Razumovsky, Saratov, Russia

Mukhtar Dzheiranov

Department of Pediatrics, Clinical Institute of Children's Health, Saratov State Medical University named after V.I. Razumovsky, Saratov, Russia.

Maleika Elnurovna Garaeva, Turkan Kamandar kizi Sharifova, Fizze Ruslanovna Zaidova, Kseniya Romanovna Korovko, Olga Vladimirovna Belyakova, Askar Satkalievich Chumbaev

Department of Medicine, Institute of Clinical Medicine, Saratov State Medical University named after V.I. Razumovsky, Saratov,

Diana Magomedovna Madagova

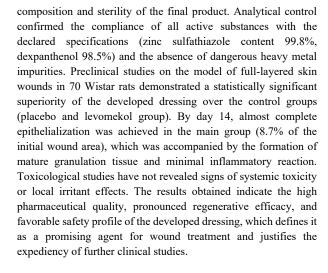
Department of Therapy, Faculty of Medicine, Chechen State University named after A.A.Kadyrov, Grozny, Republic of Chechnya, Russia.

Andrey Viktorovich Matyukhin

Department of International Relations and Foreign Policy of Russia, Institute of International Relations and Socio-Political Sciences (faculty), Moscow State Linguistic University, Moscow, Russia.

Department of Social Sciences and Humanities and Technologies, National Research Moscow State University of Civil Engineering, Moscow, Russia

*E-mail: bucky99@yandex.ru



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Introduction

The problem of effective and rapid wound healing remains one of the most urgent in modern clinical medicine, surgery, combustiology, and gerontology (Freedman et al., 2023; Peña & Martin, 2024). Chronic wounds, such as trophic ulcers, pressure sores, diabetic feet, as well as extensive burns and traumatic injuries, pose a serious medical and social problem (Ko et al., 2021; Sorg & Sorg, 2023). They significantly worsen the quality of life of patients, require long-term and expensive treatment, and create a significant burden on the healthcare system (Zhou et al., 2022). Traditional dressing methods using dry or antiseptic gauze swabs are often not effective enough. They can adhere to the wound surface, causing mechanical injury to the newly formed granulation tissue matrix and epithelium when changing the dressing, which is painful for the patient and slows down the overall regeneration process (Freedman et al., 2023; Mahmoudi et al., 2023; Zhang et al., 2023; Milcheski et al., 2025; Nur et al., 2025). In addition, the passive nature of such bandages does not create optimal conditions for wet healing, which is recognized as the gold standard in modern wound therapy (Mahmoudi et al.,



2023). The moist environment promotes the active migration of keratinocytes, stimulates angiogenesis, and autoolytic cleansing of the wound from necrotic tissues (Nuutila & Eriksson, 2021).

In light of these challenges, a promising direction is the development of ready-to-use dressings that not only protect the wound from secondary infection but also actively modulate the repair processes (Blinov et al., 2022). Our innovative development is a sterile gauze dressing impregnated with a multicomponent medicinal composition, which is ready for immediate use after opening the individual package. This approach minimizes preparatory manipulations, ensures standardized dosing of active ingredients, and creates an ideal environment for healing. The relevance of this work is due to the need to create a complex drug that combines antimicrobial properties, powerful anti-inflammatory activity, and direct stimulation of regenerative processes.

The pharmacological effectiveness of the developed dressing is provided by a unique combination of three highly active substances that interact synergistically with each other: zinc sulfathiazole, dexpanthenol, and tea tree essential oil (Shin *et al.*, 2021; Kairey *et al.*, 2023). Each of these components contributes to the overall therapeutic outcome by influencing various links in the pathogenesis of the wound process.

Zinc sulfathiazole is a key component providing antibacterial protection and a foundation for tissue proliferation (Jiang et al., 2024; Agren, 2025). This compound combines the properties of a sulfonamide antibacterial drug and the trace element zinc. Sulfathiazole exhibits a wide range of bacteriostatic effects, effectively inhibiting the growth and reproduction of both Grampositive and Gram-negative microorganisms, which is especially important in the treatment of infected wounds. Its mechanism of action is based on competitive antagonism with paraaminobenzoic acid and inhibition of dihydropteroate synthetase, which disrupts the synthesis of folic acid, necessary for the vital activity of bacteria. Zinc ions, which are part of the molecule, play an indispensable role in the processes of cell division and differentiation (Malakar et al., 2023). Zinc is a cofactor of more than 300 metalloenzymes, including DNA and RNA polymerases, which are critically important for replication and transcription in rapidly proliferating wound surface cells (Ashmawy & Azzazy, 2023). In addition, zinc helps to stabilize cell membranes, exhibits antioxidant activity, and modulates the immune response, reducing the intensity of the inflammatory response. Thus, zinc sulfathiazole not only fights infection but also creates biochemical prerequisites for accelerated epithelialization (Al-Khafaji et al., 2022).

Dexpanthenol, the second central component of the composition, acts as a direct regeneration stimulator and humidifier (Küba et al., 2021; Weßollek et al., 2023; Hashemi et al., 2024). In skin cells, dexpanthenol, being provitamin B5, is rapidly converted into pantothenic acid, an essential component of coenzyme A. Coenzyme A occupies a central place in the metabolism of all living cells, participating in key reactions of the tricarboxylic acid cycle, the synthesis of acetylcholine, steroid hormones, and porphyrins (Barritt et al., 2024). At the level of the wound process, this means activating cellular respiration and providing energy to

fibroblasts and keratinocytes. Dexpanthenol stimulates the proliferation of these cells and the synthesis of the main structural proteins, collagen and elastin, which form a strong and elastic scar tissue matrix (Fonseca *et al.*, 2020). An important property of dexpanthenol is its pronounced moisturizing and softening effect (Cho *et al.*, 2022). It helps to restore the lipid barrier of the skin and retain moisture in the tissues, which prevents the wound and the surrounding skin from drying out, maintaining optimal moisture levels for healing. This minimizes the risk of cracks and additional damage along the edges of the wound (Bagheri *et al.*, 2023).

To enhance the antimicrobial barrier and add additional properties to the composition, natural tea tree essential oil is included in its composition (Castro et al., 2021). This oil, obtained by steam distillation from the leaves of the Australian plant Melaleuca alternifolia, has a powerful, widely documented antiseptic, antifungal, and anti-inflammatory effect (Kumari et al., 2022; Pavlenko et al., 2024). Its activity is due to a complex of terpenes, among which terpinene-4-ol plays a key role (Macchia et al., 2022). This substance destroys the cell membranes of bacteria and fungi, leading to the lysis of microorganisms. Of particular value is its effectiveness against Staphylococcus aureus strains, including methicillin-resistant forms, which often colonize chronic wounds and cause serious complications (Wei et al., 2022; Nguyen et al., 2023). In addition to its direct antimicrobial effect, tea tree essential oil modulates the inflammatory response by suppressing the activity of inflammatory mediators such as tumor necrosis factor alpha and prostaglandins (Oliveira et al., 2024). This helps to reduce swelling, hyperemia, and pain in the wound area. In addition, its light fragrance has a deodorizing effect, which is extremely important for patients with wounds accompanied by an unpleasant odor caused by the activity of anaerobic microflora (Şahin et al., 2023).

The purpose of this work was to develop an innovative wound healing drug in the form of a ready-to-use impregnated gauze dressing and a comprehensive experimental assessment of its pharmaceutical quality, therapeutic efficacy, and biological safety.

Materials and Methods

The development and research of an innovative wound healing dressing was carried out in several successive stages, including the technological production process, analytical quality control, and a complex of preclinical studies based on a biological model.

Production Technology and Formulation of the Drug

The basis for the creation of the finished drug was a sterile hygroscopic gauze cloth made of 100% bleached purified cellulose cotton, conforming to pharmacopoeial standards. The drug impregnation was formed on a hydrophilic ointment base consisting of a mixture of polyethylene oxides (PEO) with different molecular weights, which ensured optimal rheological consistency, high bioavailability of active ingredients, and stability of the composition during the declared shelf life. The formulation was strictly standardized. Two hundred milligrams of highly purified zinc sulfathiazole, fifty milligrams of pharmacopoeiagrade dexpanthenol, and ten milligrams of standardized Melaleuca

alternifolia essential oil with a terpinene-4-ol content of at least thirty-five percent were used per square decimeter of impregnated gauze. The technological process of impregnation was carried out under aseptic conditions. First, a homogeneous ointment base was prepared by melting PEO in a water bath at a controlled temperature not exceeding sixty degrees Celsius. Then zinc sulfathiazole and dexpanthenol were successively added to the molten base with constant stirring until completely dissolved and dispersed. At the final stage of cooking, tea tree essential oil was introduced into the base cooled to forty degrees. The finished hot mass was applied in a thin layer to a pre-unwound and cut gauze base using special calibration equipment to ensure uniform impregnation distribution. After cooling and solidification of the ointment composition, the dressings were packaged in individual sterile three-layer combined packages made of foil and polymer materials, providing tightness and protection from UV radiation. Each batch of finished products was marked and passed the mandatory entrance control.

Analytical Quality Control and Research on the Components of the Substance

Each production batch of dressings has been subjected to a comprehensive analytical study to confirm compliance with the stated specifications and eliminate contamination with potentially dangerous impurities. Qualitative and quantitative analysis of the active substances was carried out by high-performance liquid chromatography (Hameedat et al., 2022). To do this, the dressing sample was extracted in a suitable solvent, after which the resulting solution was chromatographed, identifying and quantifying zinc sulfathiazole and dexpanthenol by peak area at a wavelength of two hundred and fifteen nanometers. The content and composition of terpenes in tea tree essential oil were controlled by gas chromatography with mass spectrometric detection (Choudhury et al., 2025). Special attention was paid to testing for the presence of heavy metals and toxic elements. The dressing samples were mineralized in a microwave decomposition system with the addition of nitric acid. The obtained solutions were analyzed by inductively coupled plasma mass spectrometry (Klika et al., 2024). Concentrations of elements such as mercury, arsenic, lead, and cadmium in all the samples studied were significantly below the thresholds established by the pharmacopoeia for dosage forms for external use. Additionally, microbiological control was carried out, which included tests for sterility by membrane filtration and determination of total microbial contamination (Neuhaus et al., 2023). All analyses confirmed the compliance of the finished product with the requirements for purity, content of active substances, and microbiological safety.

Preclinical Studies Based on a Biological Model

To evaluate the in vivo toxicological profile and regenerative efficacy of the developed drug, a study was conducted on seventy sexually mature Wistar rats with an initial body weight of two hundred and twenty-five grams. The animals were divided into five groups of fourteen individuals each, taking into account the principle of randomization. The first group of animals was treated with a developed experimental dressing with a full complex of active substances on the simulated wound. The second group was

treated with a bandage with a base, but without active ingredients, which made up the placebo control group. The third group was treated with a commercially available wound healing agent based on levomecol ointment for comparative analysis. The fourth group served as a negative control, where wounds remained without any medical treatment. The fifth group was selected for an extended toxicological study to assess the potential systemic and local irritant effects of the drug. A model of a full-layered skin wound with an area of two square centimeters was created under inhaled isoflurane anesthesia in compliance with all the rules of asepsis and antisepsis in the area of the animal's back, previously freed from hair. Bandages were changed daily.

The effectiveness of healing was assessed according to a set of parameters. A planimetric analysis of the wound surface was performed daily using digitally calibrated photography and specialized software to calculate the percentage of reduction in the wound area relative to the initial one. Histological examination was performed on the seventh and fourteenth days of the experiment. Fragments of the wound edges with adjacent tissues were fixed in ten percent neutral formalin, embedded in paraffin, and sections five micrometers thick were prepared and stained with hematoxylin and eosin, as well as using the Van Gieson method for imaging collagen fibers (Huang et al., 2012). Histological preparations were examined under a light microscope, assessing such indicators as the thickness of granulation tissue, the density and orientation of fibroblasts, the degree of neovascularization, the presence and nature of inflammatory infiltrate cells, as well as the maturity of newly formed collagen. The toxicological assessment included a daily clinical examination of the animals, registration of behavioral reactions, and water and feed intake. On the twenty-first day of the experiment, all animals were removed from the experiment using a humane method under deep anesthesia, followed by blood sampling for extensive biochemical and hematological analysis, as well as internal organs for macro- and micropathological examination in order to identify possible signs of systemic toxicity. Statistical data processing was carried out using parametric and nonparametric methods using specialized software with a significance level of p < 0.05.

Results and Discussion

The results of the conducted studies demonstrate the pronounced effectiveness and high safety profile of the developed innovative dressing. The data obtained during the experiment are systematized in the tables below. **Table 1** shows the results of the analytical quality control.

Table 1. Results of quantitative analysis of active substances and control for impurities (n=5, $M \pm m$)

Analyzed Parameter	Result Obtained	Pharmacopoeia Requirements
Content of Zinc Sulfadiazine, % of declared	99.8 ± 1.2%	95.0-105.0%
Content of Dexpanthenol, % of declared	$98.5 \pm 0.9\%$	95.0-105.0%
Content of Terpinen-4-ol in essential oil, %	$38.2 \pm 1.5\%$	Not less than 35.0%
Content of heavy metals, ppm:		

- Lead (Pb)	< 0.5	Not more than 10
- Arsenic (As)	< 0.3	Not more than 5
- Mercury (Hg)	< 0.1	Not more than 3
- Cadmium (Cd)	< 0.1	Not more than 5
Total microbial count, CFU/g	< 10	Not more than 100
Sterility	Complies	No growth

The results of the analytical control presented in Table 1 confirm the high quality and compliance of the finished product with the established specifications. The quantitative content of all active substances was within strictly defined limits, which indicates the correctness of the developed production technology and the stability of the finished dosage form. Test results for hazardous elements and heavy metals are especially significant. It was discovered that the levels of lead, arsenic, mercury, and cadmium were much below acceptable pharmacopoeial norms and at the method's sensitivity limit. This eliminates the potential cumulative toxic effects and risks associated with prolonged use of the drug, which is especially important for the treatment of chronic wounds. The results of microbiological control confirmed both the compliance of the "Total microbial contamination" indicator and the sterility of the finished packaged dressings, which guarantees safety and prevents secondary contamination of the wound surface.

Table 2 shows the results of preclinical studies using a biological model.

Table 2. Dynamics of reduction of the wound surface area in Wistar rats ($M \pm m$, % of the initial area)

Animal Group	Day 3	Day 7	Day 14
Experimental Group	85.2 ± 3.1	52.4 ± 4.2	8.7 ± 1.5
Placebo Group	98.5 ± 2.8	89.6 ± 3.8	65.3 ± 5.1
Levomecol Group	88.7 ± 3.5	60.1 ± 4.0	15.3 ± 2.2
Negative Control	99.1 ± 1.5	90.2 ± 4.5	70.1 ± 4.8

As can be seen from **Table 2**, the most intense reduction in wound area was observed in the experimental group. By the third day, the animals of this group showed a statistically significant decrease in the wound area compared to all other groups. By the seventh day, the wounds in the experimental group had more than halved, while in the placebo and negative control groups, the wound area remained close to the initial area. By the fourteenth day, at the end of the main phase of the experiment, almost complete epithelialization was observed in the experimental group (8.7%), which significantly exceeded the results of the group receiving standard levomecol therapy (15.3%), and was radically different from those of the control groups.

 $\label{thm:conditional} Table \ 3 \ \text{shows the results of the histological assessment.}$

Table 3. Results of histological evaluation of tissues on the 7th and 14th days of the experiment (scores, $M \pm m$)

Histological Parameter	Group	Day 7	Day 14
	Experimental	1120.5 ± 85.7	480.3 ± 45.2
Granulation Tissue Thickness (μm)	Placebo	450.3 ± 65.4	350.8 ± 40.1
	Levomecol	980.7 ± 79.2	420.6 ± 50.8
	Experimental	2850 ± 210	1250 ± 150

Fibroblast Density (cells/mm²)	Placebo	950 ± 180	800 ± 120
	Levomecol	2450 ± 190	1100 ± 140
Intensity of Inflammatory Infiltrate (scores 0-3)	Experimental	1.2 ± 0.3	0.3 ± 0.1
	Placebo	2.8 ± 0.2	1.8 ± 0.3
	Levomecol	1.5 ± 0.3	0.7 ± 0.2
Collagen Maturity Degree (scores 0-3)	Experimental	1.8 ± 0.2	2.7 ± 0.2
	Placebo	0.5 ± 0.1	1.2 ± 0.2
	Levomecol	1.5 ± 0.3	2.3 ± 0.3

Histological analysis (Table 3) provided a deep understanding of the cellular processes underlying the observed healing. On the seventh day, the experimental group recorded the maximum thickness of granulation tissue and the highest density of fibroblasts, which indicated an intense proliferative phase. In addition, the degree of inflammatory infiltration was low, suggesting that inflammation was effectively reducedIn the placebo group, on the contrary, there was a thin layer of granulations with low cell density and pronounced leukocyte infiltration. By the fourteenth day, an almost complete reorganization of the tissue occurred in the experimental group: the thickness of the granulation layer decreased due to the maturation and thickening of the scar, and the density of fibroblasts decreased to the level characteristic of normal skin. The key indicator was the degree of collagen maturity, which was maximal in the experimental group, indicating the formation of strong and correctly oriented collagen fibers that ensure high strength of the forming scar.

Table 4 shows the indicators of the toxicology of the innovative drug.

 $\textbf{Table 4.} \ Indicators \ of systemic \ toxicology \ and \ local \ tolerability \ on \ day \ 21$

Parameter	Experimental Group	Placebo Group	Reference Values for Wistar Rats
Body weight, g (gain)	48.5 ± 5.2	46.8 ± 4.9	45-55
ALT activity, U/L	35.2 ± 4.1	33.8 ± 3.9	20-40
AST activity, U/L	85.5 ± 7.3	82.1 ± 6.8	70-120
Creatinine level, µmol/L	45.1 ± 3.5	44.3 ± 3.2	40-60
Leukocytes, ×10°/L	8.5 ± 1.2	8.9 ± 1.1	6.0-12.0
Signs of local irritation (hyperemia, edema)	Absent	Absent	-
Pathological autopsy data	No pathology detected	No pathology detected	-

The data presented in **Table 4** convincingly demonstrate the absence of systemic toxicity and good local tolerance of the developed dressing. The indicators of body weight gain, biochemical markers of liver function (ALT, AST) and kidneys (creatinine), as well as hematological parameters in the animals of the experimental group, had no statistically significant differences from the placebo group and were within the physiological norm for

this type of animal. There were no signs of local irritation or pathological changes in the internal organs during visual examination and autopsy.

The results obtained allow for a comprehensive discussion of the mechanisms of action and benefits of the developed complex dressing. Confidence in the pharmaceutical quality of the drug, confirmed by strict analytical control data (**Table 1**), is the basis for interpreting its biological activity. The standardized composition, the absence of toxic impurities, and microbiological purity ensure that the observed therapeutic effects are the result of the targeted action of the claimed active ingredients, and not an artifact or result of contamination.

Such a pronounced superiority in the rate of reduction of the wound area in the experimental group is a direct consequence of the synergistic effect of all components of the formulation. The rapid onset of epithelialization, observed by the third day, can be explained by the combined effect of dexpanthenol and zinc ions (Weiss et al., 2019; Gorski et al., 2020; Ye et al., 2020). Dexpanthenol, being transformed into pantothenic acid, acts as a powerful metabolic stimulator, providing fibroblasts and keratinocytes with energy and cofactors for active division and synthesis of the extracellular matrix (Baron et al., 2020; Scott et al., 2022; Jin et al., 2025). Zinc ions delivered by zinc sulfathiazole act as essential cofactors of key enzymes involved in DNA replication and RNA transcription, which is a fundamental condition for any proliferative activity (Rudolf & Rudolf, 2017). Thus, these two components create ideal biochemical prerequisites for accelerated regeneration.

Histological data shed light on the qualitative characteristics of the emerging tissue. The maximum thickness and cellular density of granulation tissue on the seventh day in the experimental group directly correlated with the proliferative stimulus described above. However, it is equally important that this active proliferation occurred against the background of a minimal inflammatory reaction. This is the result of the targeted anti-inflammatory action of the components. Zinc sulfathiazole, effectively suppressing the bacterial load, eliminates the main incentive for maintaining inflammation. Tea tree essential oil, in turn, thanks to terpinen-4ol, directly inhibits the synthesis of pro-inflammatory cytokines. Relief of the inflammatory phase is critically important for a timely transition to the proliferation and remodeling phase, since prolonged inflammation not only causes additional tissue damage, but also produces enzymes that destroy the newly formed matrix (AlShammasi et al., 2024; Ravoori et al., 2024).

The high degree of collagen maturity recorded in the experimental group by the end of the experiment indicates that the developed drug not only accelerates healing but also promotes the formation of a more complete scar (Hinz, 2016; Fernandes *et al.*, 2022; Gardeazabal & Izeta, 2024). This effect is also complex. Zinc is a cofactor of the enzyme lysyl oxidase, which catalyzes the crosslinking of collagen and elastin molecules, giving connective tissue strength and elasticity. Dexpanthenol, stimulating the synthetic activity of fibroblasts, provides a sufficient amount of collagen substrate for subsequent maturation. Reducing bacterial load and inflammation prevents collagen degradation under the

action of bacterial proteases and matrix metalloproteinases released by neutrophils (Enwa et al., 2022; Savva et al., 2023).

An important aspect is the comparison with levomekol, which is a widely used standard of treatment for infected wounds (Nurul Fitri Marzaman *et al.*, 2022; Roska *et al.*, 2022; Savencu *et al.*, 2024). Although levomekol (chloramphenicol + methyluracil) also showed good efficacy, its results were statistically significantly lower in all parameters than those of the experimental drug. It can be assumed that the antibacterial component of levomecol (chloramphenicol) effectively fights infection, and methyluracil stimulates proliferation. However, it lacks a component similar to zinc, which purposefully improves collagen maturation, as well as a powerful natural anti-inflammatory agent similar to tea tree oil. This makes the developed dressing a more balanced and multipurpose tool that affects all key stages of the wound process simultaneously.

Finally, the data from the toxicological study confirm that such a pronounced therapeutic effect was achieved without any harm to safety. The absence of changes in biochemical and hematological parameters, as well as signs of local irritation, indicates that the active ingredients in the concentration used act locally without having a systemic effect on the body. This, combined with the data on the absence of toxic elements, makes the proposed dosage form safe for potential clinical use.

Thus, the totality of the results obtained allows us to conclude that the developed innovative dressing meets all pharmaceutical quality standards, has a pronounced wound healing activity exceeding the existing standard, and has a high safety profile, which opens up prospects for its further implementation in clinical practice.

Conclusion

The data obtained confirm that the developed formulation and technological process ensure high and stable pharmaceutical quality of the final product. The quantitative content of the active ingredients corresponded to the stated specifications: zinc sulfathiazole – 99.8%, dexpanthenol – 98.5%, and the content of the key component of the essential oil, terpinene-4-ol, was 38.2%. It is extremely important to confirm the purity of the drug, in particular, the absence of dangerous heavy metal impurities in its composition. Lead, arsenic, mercury, and cadmium concentrations were all well below permissible pharmacopoeial criteria, removing the possibility of cumulative toxicity from extended use (Özatik *et al.*, 2023; Ikhile & Enabulele, 2023; Shahzan *et al.*, 2023; Bona & Lozano, 2024; Figueroa-Valverde *et al.*, 2024; Suchy & Jurkowski, 2024).

The results of preclinical studies on the model of full-layered skin wounds in Wistar rats clearly indicate a pronounced regenerative activity of the dressing. The key result is a statistically significant superiority in the rate of reduction of the wound surface area compared to all control groups, including the group receiving standard levomecol therapy. By the fourteenth day of the experiment, almost complete epithelialization was achieved in the experimental group, with an index of 8.7%, which was more than seven times higher than the result in the placebo group (65.3%) and almost twice as high as the result in the levomekol group (15.3%).

Histological analysis provided a deep understanding of the cellular mechanisms underlying the observed effect. It has been established that the use of the developed dressing leads to the formation of a full-fledged, mature granulation tissue. On the seventh day, the thickness of the granulation layer in the experimental group reached 1120.5 microns, which was more than twice as high as in the placebo group. At the same time, the intensity of the inflammatory infiltrate was minimal (1.2 points versus 2.8 points in the placebo group), which confirms the powerful antiinflammatory and antimicrobial effects of the composition. By the final stage of the experiment, the maximum degree of collagen maturity was recorded in the experimental group, 2.7 points, which indicates the formation of a durable and elastic scar (Ruchin et al., 2022; Rudayni et al., 2022; Spirito et al., 2022; Sugimori et al., 2022; Bulusu & Cleary, 2023; Kiedrowicz et al., 2023; Kulkarni et al., 2023; Dorn et al., 2024; Mao et al., 2024).

The most important aspect of the work carried out is the proof of the high safety profile of the drug. The toxicological examination data did not reveal any signs of systemic toxicity or local irritant effects. The indicators of biochemical and hematological analysis in the animals of the experimental group remained within the physiological norm, without statistically significantly differing from the placebo group.

Thus, the totality of the results obtained – from confirmation of pharmaceutical quality to demonstration of efficacy and safety in vivo – allows us to conclude that the developed innovative dressing is a promising tool for the treatment of wounds of various etiologies. The combination of antimicrobial, anti-inflammatory, and powerful regenerative properties provided by the synergism of zinc sulfathiazole, dexpanthenol, and tea tree essential oil surpasses the capabilities of existing standard therapeutic approaches. The results obtained are a solid basis for planning subsequent clinical trials with the aim of introducing this drug into widespread medical practice.

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Conflict of interest: None

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Ethics statement: All experimental procedures involving animals were conducted in strict accordance with the international principles of the Basel Declaration and the guidelines for the ethical treatment of animals in biomedical research. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee. All efforts were made to minimize animal suffering and to reduce the number of animals used, while maintaining scientific validity. Procedures were performed under appropriate anesthesia, and all necessary measures were taken to ensure humane endpoints throughout the study duration.

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