ORIGINAL ARTICLE

A pharmacodynamic study of a new gel containing an extract of *Aloe vera* and an extract of oak bark for potential treatment of periodontal diseases

Farmakodynamická studie nového gelu obsahujícího extrakt z *Aloe vera* a extrakt z dubové kůry pro potenciální léčbu onemocnění parodontu

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Summary

The article presents the results of a pharmacodynamic study of a new gel containing an extract of *Aloe vera* and an extract of oak bark under the condition of destructive inflammatory periodontal diseases. Pharmacodynamics of the new gel was studied by the following methods: antimicrobial effect – by diffusion method in agar gel (compared product – Metrogyl denta® gel); reparative effect – on the model of linear cut wounds (compared product – *Calendula* ointment); anti-inflammatory activity – on the model of acute carrageenan-induced inflammation (compared product – *Diclofenac natrium gel* 5%). It has been established that the antimicrobial activity of the new gel against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* NCTC 885-653, *Escherichia faecalis* ATCC 29212, and *Staphylococcus mutans* ATCC 35668 is slightly lower in comparison with Metrogyl denta® gel exhibiting a powerful antimicrobial activity. According to the reparative effect on the model of linear cut wounds, the new gel exceeded the effectiveness (by 24%, $p < 0.001$) of the compared drug based on the medicinal plant material – *Calendula* ointment. A significant anti-inflammatory activity of the new gel has been revealed under the conditions of acute carrageenan inflammation. It exceeded the *Diclofenac natrium* gel in the first hours of the experiment, indicating an anti-lipoxygenase activity of the new gel. The established antimicrobial, reparative and anti-inflammatory activity of a new gel containing aloe vera and oak bark extracts confirmed its potential use in the treatment of destructive inflammatory periodontal diseases.

Key words: destructive-inflammatory periodontal disease • gel • oak bark extract • aloe vera extract

Souhrn

Článek prezentuje výsledky farmakodynamické studie nového gelu obsahujícího extrakt z *Aloe vera* a extrakt z dubové kůry v podmínkách destruktivního zánětlivého onemocnění parodontu. Farmakodynamika nového gelu byla studována následujícími metodami: antimikrobiální účinek – difuzní metodou v agarovém gelu (srovnávaný produkt – Metrogyl denta® gel); reparativní účinek – na modelu lineárních řezných ran (srovnávaný produkt – měsíčková mast); protizánětlivá aktivita – na modelu akutního zánětu vyvolaného karagenanem (srovnávaný produkt – 5% gel sodné soli diklofenaku). V rámci studie bylo zjištěno, že antimikrobiální aktivita nového gelu proti *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* NCTC 885-653, *Escherichia faecalis* ATCC 29212. *Staphylococcus mutans* ATCC 35668 byla mírně nižší ve srovnání s gelem Metrogyl denta®, který vykazuje silnou antimikrobiální aktivitu. Podle reparativního účinku na modelu lineárních řezných ran vykazoval nový gel vyšší účinek (o 24 %, $p < 0.001$) ve srovnání s přípravkem na bázi léčivého rostlinného materiálu měsíčkovou mastí. Za podmínek akutního zánětu vyvolaného karagenanem byla prokázána významná protizánětlivá aktivita nového gelu. Přípravek překonal gel sodné soli diklofanaku v prvních hodinách experimentu, což ukazuje na anti-

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lipooxygenázovou aktivitu nového gelu. Zjištěná antimikrobiální, reparativní a protizánětlivá aktivita nového gelu obsahujícího extrakty z *Aloe vera* a dubové kůry potvrdila možnost jeho použití při léčbě destruktivních zánětlivých onemocnění parodontu.

Klíčová slova: destruktivní zánětlivé onemocnění parodontu • gel • extrakt z dubové kůry • extract z aloe vera

Introduction

According to the World Health Organization (WHO) epidemiological data, the destructive-inflammatory periodontal diseases, which in the first category include stomatitis, gingivitis and periodontitis (aggressive and chronic), are extremely widespread among the population (up to 90%), adversely affecting the general functional and psychological state of a person and being an underestimated problem of modern medicine[1]. These diseases in many cases are an insurmountable problem for oral health and positively correlate with chronic systemic pathologies. Thus, in the Consensus Report of the Third All-Seminar on Periodontal Disease[2] on the basis of evidence-based medicine, it has been proved that metabolic syndrome, diabetes mellitus, osteoarthritis, cancer, etc., have a significant effect on the periodontal apparatus. Periodontitis associated with them should not be considered as a separate diagnosis, but systemic diseases should be recognized as important modifying factors and included in the clinical diagnosis of periodontitis as descriptors.

Despite the improvement of the methods of prevention and treatment, the number of patients with destructive–inflammatory diseases of the periodontium and oral cavity in certain groups of patients (elderly, concomitant diseases) reaches 90%. Therefore, the optimization of the treatment of periodontal diseases and oral cavity diseases, and the search for new drugs is an urgent task of modern pharmacy and medicine[3, 4].

An assortment of medicines that would have a modal pharmacological activity, especially antibacterial, reparative, and anti-inflammatory is extremely limited. One of the promising directions in this area is the use of medicinal products on the basis of medicinal plant material, which has polymodal pharmacological effects on various parts of the pathological process, low toxicity, and can be used for different age groups[5].

Current urgent issues are the development of new complex drugs that can affect the pathogenetic links of inflammatory diseases of the oral cavity.

NUPh scientists under the direction of Dr. Pharm. N.V. Khokhlenkova developed a new gel containing an extract of aloe vera and an extract of oak bark, which may be promising in the aspect of research and development of a new medicinal product for the treatment of destructive--inflammatory diseases of periodontium and oral cavity[6].

In the work of Panchal et al., cardioprotective and hepatoprotective effects of elagitanins from European oak extract were studied. Oak bark extract reduced the signs of metabolic syndrome in high-carbohydrate diets in rats and improved the structure and function of the heart and liver. It has been found that oak bark extract weakens the signs of metabolic syndrome and improves the structure and function of the heart and liver[7].

In the study by Bhatia et al., animal and human studies have been performed that positively characterize the antibacterial, wound-healing and anti-inflammatory properties of oak bark extract[8].

Dong et al. had conducted an analysis of the pharmacology, toxicity, and pharmacokinetics of aloe-emodin. The results of the analysis revealed that aloe-emodin exhibits many pharmacological effects, including anti-cancer, antiviral, anti-inflammatory, antibacterial, antiparasitic, neuroprotective and hepatoprotective effects[9].

Shakib et al. investigated the pharmacological effects of aloe on various components of the metabolic syndrome. The aloe gel exhibits anti-inflammatory, antioxidant, antiviral, antibacterial, and wound healing properties. Aloe effects such as lipid lowering, antihypertensive, antidiabetic, anti-vital and cardioprotective effects have also been reported in several studies[10].

In the work of Haque et al., the antibacterial effect of the gel based on an ethanol extract of aloe vera leaf was studied against the standard strains of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumonia*. It has confirmed an antibacterial action of the gel against the investigated pathogens[11].

The aim of this work was to study the pharmacodynamics of a new gel containing aloe vera and oak barks extracts, namely its antimicrobial, reparative, and anti-inflammatory activity.

Experimental part

Materials

The new gel composition: the dry aloe vera extract (3%) (TU 24.5-31342973017: 2010, production of PJSC (Red Star Chemical Factory, Ukraine), the thick oak bark extract (5%) (EF 5.0, production of GFL Ltd Pharmaceutical Company, Georgia). Excipients: glycerol, Carbopol®, saccharin sodium, trometamol, nipagin (Ukraine).

The compared drugs used were the well-known antibacterial drug Metrogyl denta® gel (Unic Pharmacist Laboratories, India, series № PGF2131216), *Calendula* ointment (PRAT Phytopharm Ukraine, Serial № 40219 08 21), Diclofenac natrium gel 5% (LLC Pharmaceutical company Zdorovya, Ukraine, series № 490718).

Methods

Animals were kept under the same conditions, with a standard diet, in accordance with the sanitary--hygienic requirements of the Central Scientific-Research Laboratory (CSRL) NUPh vivarium (certificate № 058/15 dated 12.08.2015, valid until 07.12.2019). All experiments were carried out in accordance with the general ethical principles of animal experimentation,

regulated by the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986, with amendments, 1998) and the Law of Ukraine № 249 dated 01/03/2012 "Procedure for carrying out scientific experiments and experiments on animals by scientific institutions".

Experimental studies of the pharmacodynamics containing aloe vera (3%) and oak bark (5%) extracts were performed in three stages.

Study of the antimicrobial activity by the standard method of diffusion into an agar gel

Firstly, the antimicrobial activity of the new gel was studied by the standard method of diffusion into an agar gel, according to the State Pharmacopoeia of Ukraine.

According to the WHO recommendations, for the evaluation of the activity of the drug, reference cultures of *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* NCTC 885-653 and specific pathogens for *Escherichia faecalis* ATCC 29212 and *Staphylococcus mutans* ATCC 35668 are recommended. For the results evaluation, the following criteria were taken into account: the absence of zones of inhibition of the growth of reference crops around the wells; zones of growth retardation of microorganisms up to 11 mm indicate the insensitivity of microorganisms to the drug introduced into the well; growth retardation zones of reference cultures with a diameter of 11–15 mm indicate a low sensitivity of culture; zones with a diameter of 15–25 mm are evaluated as an indicator of the sensitivity of microorganisms to the drug; areas of inhibition of the growth of reference crops, which exceed 25 mm – high sensitivity of microorganisms to the medicinal product. As the comparison drug, the well-known anti-bacterial drug Metrogyl denta® was used.

Study of the reparative effect on the model of linear cut wound

At the second stage, the reparative effect of the new gel was studied on the model of linear cut wounds, which was reproduced in the following way. Animals under anaesthesia under aseptic conditions were made a 5 cm length incision to their own fascia on a depilated area of the skin of the spine with an area of 5 × 3 cm^2. Immediately 5 sutures were applied at the distance of 1 cm from each other and treated with 5% alcohol ruby iodine. From the next day, the treatment started for 5 days. The reference medicinal products were applied once a day. On Day 6, the animals were decapitated (chloroform) and cut off the skin with a scar. On a special device wound tensiometer, a rumen strength test was performed. One edge of the seam was fixed in a stationary clamper, and the other in a clamper with a load (capacity with water). Evenly pouring water into a container determined the mass at which the seam diverged, which corresponds to the rumen strength. Reparative activity (*RA*) of the drug was determined by the formula [1]:

$$RA = (M_e – M_c)/M_e \times 100, \quad [1]$$

where M_e – load, at which the suture diverged in the rats of the experimental group, g; M_c – load, at which the suture diverged in the group of control pathology, g.

The study was conducted on white non-linear rats weighing 180–230 g, which were distributed to the following experimental groups (n = 8): 1st group: control pathology; 2nd group: animals that received the new gel; 3rd group: animals used for the reference medicinal product based on medicinal plant material with a reparative effect – *Calendula* ointment.

Study of the anti-inflammatory activity on the model of acute carrageenan-induced inflammation

The third stage of the study was aimed to investigate the anti-inflammatory activity of the new gel on the model of acute carrageenan-induced inflammation by sub-planar introduction of 1% solution of carrageenan. The volume of oedema was observed in dynamics after 1, 2, 3, 4, 6 and 24 hours and measured. The anti-exudative activity (*A*) was determined by the ability to reduce the oedema in comparison with the volume of the paw in the control, calculated in %, using the formula [2]:

$$A = (V_k – V_o)/V_k \times 100\%, \quad [2]$$

where V_k – volume of paw, V_o – amount of paw in experiment.

The study was conducted on white male non-linear rats weighing 180–230 g which were divided into the following groups, (n = 8): 1st group: intact control; 2nd group: animals, which were applied to the affected paw of 0.5 ml of the new gel; 3rd group: animals, which were applied to the affected paw 0.5 ml of Diclofenac natrium gel 5%.

The experimental data received were statistically processed using the Student's test, with the aid of statistical analysis programs. Version 6. AnalystSoft Inc., StatPlus[12].

Results and discussion

The results of the antimicrobial activity of the new gel containing aloe vera and oak bark extracts are given in Table 1.

The results of microbiological studies have shown that the new gel containing an aloe vera extract and an extract of oak bark exhibited antimicrobial activity on the representatives of gram-positive reference cultures *Staphylococcus aureus* ATCC 25923, *Streptococcus mutans* ATCC 35668, *Bacillus subtilis* ATCC 6633, and gram-negative ones *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853 reference cultures. The antimicrobial activity of the new gel and specific pathogens in the mouth of *E. faecalis* ATCC 29212 and *S. mutans* ATCC 35668 has been established. Regarding the antifungal activity, it should be noted that the new

Table 1. Investigation of the antimicrobial activity of the new gel by the method of diffusion into agar gel

Pathogenic microorganism	New gel	Metrogyl denta® gel
	Diameter of the growth retardation zone, mm	
S. aureus ATCC 25923	20.17 + 0.91*	24.15 + 0.45
E. coli ATCC 25922	20.49 + 0.41*	28.47 + 0.89
B. subtilis ATCC 6633	19.68 + 0.49*	27.12 + 0.11
P. aeruginosa ATCC 27853	20.87 + 0.68*	26.51 + 0.11
C. albicans NCTC 885-653	30.42 + 0.50*	23.16 + 0.18
E. faecalis ATCC 29212	17.34 + 0.41*	24.01 + 0.82
S. mutans ATCC 35668	18.79 + 0.51*	26.41 + 0.19

* the difference in the values is probable with respect to the comparison product Metrogyl denta® gel ($p < 0.01$)

Table 2. Study of the pharmacological activity of the new gel on the model of linear cut wounds, n = 8

Experiment groups	Rumen strength, g	Reparative activity, %
Control pathology	454.13 ± 8.16	–
The new gel	720.50 ± 12.38*#	58.66
Calendula ointment	610.88 ± 8.22*	34.52

* the difference of indices is probable with respect to the group of control pathology ($p < 0.001$)
#difference of indices is probable relative to the group of preparation of comparison of *Calendula* ointment ($p < 0.001$)
n – the number of animals in the group

gel showed high sensitivity to *Candida albicans* NCTC 885-653.

The antimicrobial activity of the new gel is due to the introduction of a thick extract of oak bark, which is a complex of plant polyphenols, tannis and flobafens. By chemical structure, the tannins in the extract are hydrolyzed and condensed groups. It is known that the tannins of the extract of oak bark, namely, 4-(3-hydroxy-1-propenyl)--2-methoxy-phenol; 3,4,5-trimethoxyphenol; 4-hydroxy--3-methoxybenzaldehyde; 7-hydroxy-6-methoxy-2H--1-benzopyran-2-one and 2H-1-benzopyran-2-one, have a strong direct antibacterial effect due to the denaturation of protoplasmic proteins of pathogenic microorganisms, which impedes their development[13].

It should be noted that the antibacterial activity of the new gel based on medicinal plant material, without doubt, inferior to the effectiveness of the comparator drug Metrogyl denta® gel, a combined preparation for the comprehensive treatment of infectious and inflammatory diseases of the oral cavity. Efficiency of the Metrogyl denta® gel is ensured due to the presence of two antibacterial components – metronidazole and chlorhexidine. Metronidazole is a derivative of nitroimidazole, which exhibits antiprozen and antimicrobial activity. Chlorhexidine is an antiseptic with bactericidal action. It is active in a wide range of vegetative forms of gram-negative and gram-positive microorganisms, as well as yeasts, dermatophytes and lipophilic viruses[6].

The results of the reparative action study are presented in Table 2. It was established that application of the new gel containing the extracts of aloe and oak bark in 1.6 times increased the rumen strength with respect to the group of unlabelled animals (control pathology) on the experimental linear wound, according to the indicator, reparative activity was probable (by 24%) to exceed the efficacy of the comparator preparation *Calendula* ointment.

Thick oak bark extract has an anti-inflammatory, antimicrobial effect, aloe dry extract has pronounced reparative and antimicrobial properties. The powerful reparative activity of the new gel can be explained by its complex composition. The versatility of reparative and anti-inflammatory action of oak bark extract, according to Bhatia et al. (2019)[8] explain the effectiveness of this component in clinical dermatology.

Aloe vera extract contains antraglycosides (barbaloin, aloe-emodine, nataloid, rabarberon); resinous substances (aloezin A, aloenin A and B); carotenoids, ascorbic acid; traces of essential oils; microelements: K, Mg, Cu, Se, Zn, Li, Ba. This composition provides a wide range of pharmacological activity of the aloe extract. Across the world, aloe tree (*Aloe arborescens* Miller) has a long history of application. Thanks to its wound healing effect, aloe is widely used in cosmetology, in dermatology (for the prevention and treatment of various skin lesions), in medicine (for the prevention and treatment of ulcers of the stomach and duodenum, eye diseases, etc.)[14].

The results of the next stage of the study on anti-inflammatory action of the new gel are given in Table 3.

It has been established that due to the ability to suppress the lipoxygenase pathway of inflammatory mediators, the new gel has a pronounced anti-inflammatory activity in the first hours of carrageenan-induced inflammation, in contrast to the Diclofenac natrium gel 5%, the maximum anti-inflammatory activity (3–4 hours) is associated with the ability to inhibit cyclooxygenase[6].

Table 3. Investigation of the anti-inflammatory activity of the new gel in the carrageenan-induced inflammation, n = 8

Group	Hours of inflammation					
	1 hour	2 hour	3 hour	4 hour	6 hour	24 hour
	Volume of paws V ± Δv, cond. units					
Control pathology	17.62 ± 2.08	21.50 ± 1.53	25.62 ± 1.31	28.12 ± 1.23	31.62 ± 0.80	9.75 ± 1.33
New gel	11.75 ± 0.62*#	13.25 ± 0.94**	16.62 ± 1.24**	19.75 ± 39**##	21.5 ± 1.45***	4.0 ± 0.46**
Diclofenac natrium gel 5%	14.0 ± 0.46	16.75 ± 1.29*	14.12 ± 1.33***	13.75 ± 0.81***	22.65 ± 0.59***	6.25 ± 0.52*
Antiexudative activity, %						
New gel	33.33 %	38.37 %	35.12 %	29.77 %	32.01 %	58.97 %
Diclofenac natrium gel 5%	20.56 %	22.09 %	44.87 %	51.11 %	28.45 %	35.89 %

The difference in the rates is probable with respect to the control group: *p < 0.05, **p < 0.01, ***p < 0.001
The difference of the indices is probable with respect to the group of Diclofenac natrium gel 5% #p < 0.05, ##p < 0.01
n – the number of animals in the group

It should be noted that due to the cytoprotective and antioxidant action of the biologically active substances of the aloe vera and oak bark extracts[15,16] an increase in anti-inflammatory activity of the new gel occurs from 6 to 24 hours of experiment, in contrast to the Diclofenac natrium gel 5%.

Conclusions

The pharmacodynamic profile of the new gel containing a dry aloe extract and a thick extract of oak bark is conducted.

The new gel has a pronounced antimicrobial activity against *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* NSTC 885-653, and specific pathogens in the oral cavity *Escherichia faecalis* ATCC 29212 and *Staphylococcus mutans* ATCC35668.

The established reparative effect of the new gel on the model of linear cut wounds probably exceeds the effectiveness of the preparation used for comparison, the monocomponent composition based on medicinal plant material – *Calendula* ointment.

A significant anti-inflammatory effect of the new gel has been established, which, in conditions of acute carrageenan-induced inflammation, exceeded the 5% Diclofenac natrium gel comparison drug in the first hours of the experiment, indicating a significant anti-lipoxygenase activity of the new gel.

The complex composition of the new gel gives it considerable advantages over the comparison drugs, the established antimicrobial, reparative and anti-inflammatory action of the new gel containing aloe vera and oak bark causes the pharmacodynamic feasibility of its use in the treatment of destructively inflammatory diseases of the periodontal and oral cavity.

The new gel which contains a thick oak bark extract and a dry aloe extract can be considered a promising object for further pharmacological studies with the aim of creating a new effective parodont-protective drug.

Conflicts of interest: none.

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