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Research Article

Investigation of wound healing activity of the flavonoid schaftoside isolated from *Lychnis chalcedonica*

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Abstract

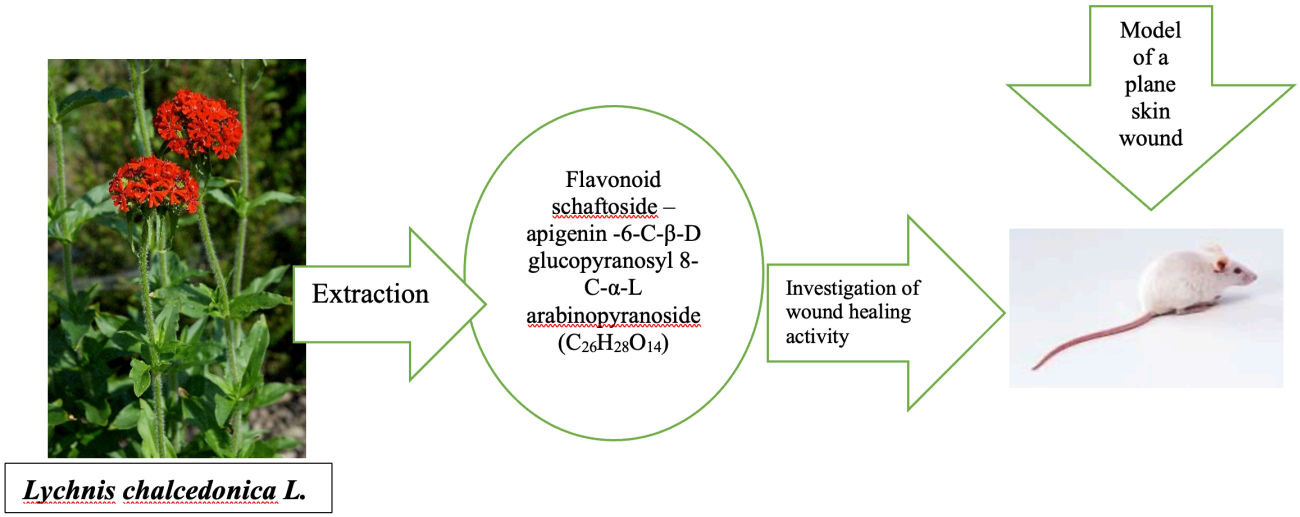
Introduction: This article studies the wound healing activity of the flavonoid schaftoside – apigenin -6-C-β-D glucopyranosyl 8-C-α-L arabinopyranoside ($C_{26}H_{28}O_{14}$) isolated from the above-ground part of *Lychnis chalcedonica* L.

Materials and Methods: The experiments were carried out on sexually mature mongrel male CD-1 mice. The wound healing effect of schaftoside was studied on a model of a plane skin wound. Schaftoside was applied externally (topically) in the form of an aqueous solution using a pipette of 100 mcl per wound at concentrations of 0.1 uG/mL, 1.5 uG/mL, 3.0 uG/mL, one time per day during the entire period of wound healing from the first day after the wound had been induced until its complete epithelialization. Aloe juice (100 mcL per wound) was used as a positive control. A solvent (water) – 100 mcL per wound – was applied to control animals.

Results and Discussion: The results of our study on the model of a plane skin wound showed that the compound schaftoside isolated from *Lychnis chalcedonica,* when applied externally (topically) at concentrations of 0.1 uG/mL, 1.5 uG/mL, 3.0 uG/mL, contributes to a significant reduction in the size of plane skin wounds, comparable to the action of aloe juice (the comparison drug). The wound healing effect is more pronounced at the first, second, and third weeks of the healing process, i.e. at the stage of inflammation, proliferation, and activation of the repair process. Under the influence of schaftoside at a concentration of 3.0 uG/mL, a more complete epithelialization was recorded than in the group where the comparison drug (aloe juice) was applied.

Conclusion: Our study for the first time shows a pronounced wound healing effect from aqueous solution of the flavonoid schaftoside from *Lychnis chalcedonica* on the model of a plane skin wound in mice.

Graphical abstract:



Investigation of wound healing activity of the flavonoid schaftoside

Keywords

plane skin wound, *Lychnis chalcedonica* L., flavonoid schaftoside

Introduction

An important task of pharmacology is to search and develop new drugs which stimulate regeneration processes. Wounds (including chronic ones) which result from diabetes, burns, venous diseases, and long-term compression syndrome are a great practical and scientific problem. When persisting for a long time, wound defects, which are a source of infection, result in a persistent pain syndrome and depressive states (Blinova et al. 2018). Models of skin wounds are the most adequate to use in experimental studies, since only in these tissues, the dynamics and mechanism of regenerative processes are traced most clearly, which makes it possible to effectively assess how the studied drugs influence them (Frolova et al. 2009). The natural healing process includes three stages: stage I – inflammation; stage II – proliferation, which is characterized by an increase in the mitotic index and activation of repair process; stage III – epithelization (Fenchin 1979; Reinke and Sorg 2012; Baron et al. 2020). The intensity of reparative regeneration depends on a large number of factors: the state of the immune system, the microcirculatory bed, and the functional capabilities of skin stromal cells (Nosenko et al. 2019).

A large number of wound healing drugs for external use are known to be made in the form of various drug dosage forms, namely ointments, emulsions, applications, and gels. Multicomponent ointments on an osmotically active basis – Levomekol and Levosin – have a complex effect on the wound surface (Mashkovsky 2012). Herbal remedies (sea buckthorn oil, kalanchoe juice, and aloe juice) are well known and still used in clinical practice. Aloe juice (Succus aloes), which accelerates the regeneration processes, is the closest in the nature of origin. It is prescribed for the treatment of festering wound, burns, inflammatory skin diseases, and peptic ulcer of the stomach and duodenum (Mashkovsky 2012; Pazyar et al. 2014; Albahri et al. 2023).

Lychnis chalcedonica (*Caryophyllaceae* family) has a wide distribution area. It grows in the European part of Russia, in the regions of Eastern Siberia and Central Asia (Rastitelniye resursy ... 1985). The flavonoid schaftoside isolated from this plant is also found in other plants: *Viola mandshurica*, *Viola yedoensis* (Petrova and Medvedeva 2020), those of the Silene genus (*Silene aprica* L., *S. italica, S. nutans, S. repens, S. samojedorum, S. schafta)* (Zibareva et al. 2021), *S. sibirica* L. (Olennikov and Kashchenko 2020), *Urtica cannabina* (Fedoseeva and Kiryakova 2017), and others (Xiong et al. 2015; Liu et al. 2017; Zhou et al. 2019). Thus, the resource base for isolation of the compound schaftoside is very large in contrast with the comparison drug (aloe tree juice).

Materials and Methods

Plant Raw Materials and Extraction

Isolation of flavonoids. Air-dry raw materials of L. *chalcedonica* (200 g) were extracted fivefold with 70% ethanol solution. The resulting extract was filtered and concentrated under vacuum at a temperature of 55°C. The concentrated extract was diluted with water in a ratio of 1:2 (v:v) and filtered again. Then the filtrate was purified from lipophilic substances three times with *n*-hexane. The control of the BAS content in fractions was carried out by the HPLC method. The isolation of the amount of secondary metabolites from the purified filtrate was carried out by repeated extraction with *n*-butanol. The yield of a dry butanol fraction was 21.2% of the dry raw material. When concentrating the butanol fraction dissolved in 80% ethanol, a yellow-brown precipitate fell out, whose yield was 1.26% of the raw material. Recrystallization of the precipitate using 70% and 95% ethanol allowed obtaining a pure compound, whose

content was 81% of the total peaks of flavonoids, or 1.02% of the raw materials.

HPLC analysis (Fig. 1) indicates that the isolated compound is an individual flavonoid with a retention time of 13.379 min.

The isolated flavonoid has two absorption maxima corresponding to two aromatic rings A and B (Fig. 2, Table 1). The individual compound was identified by HPLC, mass spectrometry, and NMR ^{1}H and ^{13}C spectroscopy (Zibareva et al. 2022).

The characteristic of the isolated individual compound – apigenin -6-C-β-D glucopyranosyl 8-C-α-L arabinopyranoside – flavonoid schaftoside ($C_{26}H_{28}O_{14}$) is presented in Table 1. The purity of the isolated compound schaftoside was 95.49%.

Table 1. Characteristics of the isolated individual compound

Flavo -noid	Gross formula	Molecu-lar mass	Peak Area, %	Absorp-tion maxi-mum, nm	Reten-tion time, min
Schaf-toside	$C_{26}H_{28}O_{14}$	564	95.4924	271; 336	13.379

Drugs

Aloe juice (CJSC VIFITECH, Russia) was selected as the comparison drug, which was used externally (topically) after de-alcoholization application of 100 mcl per wound.

Experimental animals

The experiments were carried out on conventional sexually mature mongrel male CD-1 mice of the first category provided by the Biomodeling Department of Goldberg Institute of Pharmacology and Regenerative Medicine (Tomsk, Russia). The weight of the animals ranged from 22 to 27 g. Animal welfare and the experiment plan were approved by the Bioethical Committee (the IACUC Protocol No. 95092015 dated 16.09.2015). The protocol of the study was in accordance with Directive 2010/63/EC of the European Parliament and the Council for the Protection of Animals, and Order No. 199n of the Ministry of Health of the Russian Federation as of August 1, 2016. The animals were adapted to the vivarium in a separate room 3 days prior to the experiment. Before the start, each animal in the group was assigned an individual number using body weight as a criterion.

Experimental protocol

The model of a plane skin wound was used for the study (Frolova et al. 2009). A 10x10 mm skin flap was cut out on the depilated area of the mice's backs under ether anesthesia. To simulate a longer healing time, the scab was regularly (every day) removed from the wound. The criteria for the development of pathological process were the following indicators: the average diameter of the wound, the number of animals (%) with healed wounds, acceleration of the healing time (AHT=the time of complete wound healing in the control – the time of complete wound healing in the experiment/the time of complete wound healing in the control x 100%). Based on these data, the rate of the wound diameter reduction was calculated in mm/day and per cent. When the wounds were completely healed, all animals were euthanized, and the excised wound defect was morphometrically examined: the completeness of epithelialization, thickness of the skin defect, and the presence of hair follicles were evaluated (Efimov 1975).

In the experiments, the animals were divided into the following groups: control, comparison, and experimental. A solvent (distilled water) of 100 mcL per wound was applied to the control group. In the positive control group, aloe juice of 100 mcL per wound was applied externally (topically) as the comparison drug.

In the experimental group, the animals received the proposed drug – the compound schaftoside diluted with distilled water to a concentration of 0.1 uG/mL; 1.5 uG/mL; and 3.0 uG/mL. The drug under study was applied externally (topically) in the form of an aqueous solution using a pipette of 100 ml per wound at a concentration of either 0.1 uG/mL, or 1.5 uG/mL, or 3.0 uG/mL, one time per day during the entire period of wound healing from the first day after the wound had been induced. Similarly, the solvent was applied to the control group, and aloe juice to the comparison group. The effect of the drug under study was evaluated by comparing the corresponding indicators of the experimental group animals with those of the control group and the group receiving the comparison drug (aloe juice).

Statistics

Statistical processing of the obtained results was carried out by methods of variational statistics using the IBM software. The arithmetic mean ($\bar{X}$), the error of the arithmetic mean (m), and the probability value (P) were calculated. The difference between the two compared values was considered reliable if the probability of their identity was less than 5% ($P<0.05$). The degree of approximation of the distribution law of the studied feature to the normal was estimated using sample coefficients of asymmetry and kurtosis. In cases of normal distribution of features, the parametric Student t-test was used for statistical evaluation. For large deviations of feature distributions from the normal form, a nonparametric U-test (the Wilcoxon-Mann-Whitney criterion) was used for independent samples. To compare the results of experiments where the indicators were expressed in fractions, the reliability was determined using the Fisher's angular transformation method. The significance of the differences was considered valid at $P<0.05$ (Lakin 1980). Statistica 6.0 software was used.

Results and Discussion

Treatment of the outbred male CD-1 mice started in the first hours after the wounds were inflicted and continued until complete epithelialization. During the experiment, a regular dynamics of the wound process was observed. According to the data obtained, complete wound healing was observed in mice of the control group by day 21 (Tables 2, 3).

The wounds were completely healed on day 16 in the groups of mice in which 100 mcL of schaftoside solution had been applied externally at a concentration of 0.1 uG/mL, and in the positive control group, where the mice had received the comparison drug (aloe juice) in the same volume within the course of use. A favorable dynamics was observed under the influence of these drugs; the wounds were healed 5 days earlier than in the control.

Table 2. The dynamics of change in the average diameter of wounds, cm

Time frame for study, days	Control, n=7	Aloe juice, 100 mcL per wound, n=8	Schaftoside 0.1 uG/mL, 100 mcL per wound, n=8	Schaftoside 1.5 uG/mL, 100 mcL per wound, n=9	Schaftoside 3.0 uG/mL, 100 mcL per wound, n=10
2	10.1±0.3	9.3±0.2*	9.4±0.3	9.4±0.3	9.3±0.2*
4	9.6±0.3	8.3±0.3*	8.6±0.3	8.6±0.2*	8.3±0.2*
7	8.0±0.4	6.3±0.4*	6.5±0.4*	6.7±0.4*	6.8±0.2*
9	5.8±0.5	4.4±0.4*	4.5±0.3*	4.0±0.2*	4.1±0.3*
11	3.9±0.7	2.4±0.3	3.1±0.4	2.1±0.3*	2.6±0.3
14	1.7±0.5	0.3±0.1*	0.8±0.3	0.2±0.2*	0.5±0.3*
16	0.6±0.3	0±0*	0±0*	0.1±0.1	0.1±0.1
18	0.03±0.02	0±0	0±0	0±0	0±0
21	0±0	0±0	0±0	0±0	0±0

Note: * – P<0.05 in comparison to the control group.

Table 3. The proportion of animals with healed wounds, %

Time frame for study, days	Control, n=7	Aloe juice, 100 mcL per wound, n=8	Schaftoside 0.1 uG/mL, 100 mcL per wound, n=8	Schaftoside 1.5 uG/mL, 100 mcL per wound, n=9	Schaftoside 3.0 uG/mL, 100 mcL per wound, n=10
14	14.3	62.5*	50	77.8*	60*
16	28.6	100*	100*	88.9*	80*
18	71.4	100*	100*	100*	100*
21	100	100	100	100	100
AHT, %	0	23.8	23.8	14.3	14.3

Note: * – P<0.05 in comparison to the control group; AHT – acceleration of the healing time.

The acceleration of the healing time (AHT) of wounds was 23.8% (Table 3). The proposed drug at concentrations of 1.5 mcL/mL and 3.0 mcL/mL contributed to complete wound healing on day 18.

From day 4 of the study, significant differences in the size of the wound were recorded in the group of animals to which schaftoside solution was applied, in comparison to the control group. A persistent decrease in the diameter of wounds in all experimental groups and the comparison group was shown on day 7: the average diameter of wounds was 1.2-1.3 times smaller than the control values; on day 9, it was 1.3-1.5 times smaller. This indicates the presence of a wound healing effect in schaftoside which is similar to that of the comparison drug (aloe juice) (Table 2). Moreover, schaftoside at concentrations of 1.5 and 3.0 uG/mL significantly increased the rate of wound healing in the initial period (days 2-4, Table 4).

After the visible epithelization of the wound has been completed, the process of differentiation of the epidermis still continues for a long time. The analysis of morphological processes occurring in the area of mice's wound defect on day 21 showed that in the control group, an incomplete regenerate was formed; a continuous but thin layer of epithelium was observed in most animals (Table 5).

Table 4. The dynamics of indicators in animals of various experimental groups

Time frame for study, days	Control, n=7	Aloe juice, 100 mcL per wound, n=8	Schaftoside 0.1 uG/mL, 100 mcL per wound, n=8	Schaftoside 1.5 uG/mL, 100 mcL per wound, n=9	Schaftoside 3.0 uG/mL, 100 mcL per wound, n=10
The rate of the average wound diameter reduction, mm/day					
2-4 days	1.7±0.4	3.3±0.8	2.7±0.6	3.0±0.5*	3.5±0.6*
4-11 days	7.1±0.7	7.3±0.3	7.0±0.5	8.1±0.2	7.1±0.3
11-18 days	4.9±0.8	3.1±0.4	3.8±0.5	2.6±0.4*	3.2±0.4
The rate of the average wound diameter reduction, %					
2-4 days	5.0±1.2	10.7±2.4*	8.6±1.9	9.3±1.7*	11.2±2.0*
4-11 days	59.5±6.4	71.2±3.6	64.8±4.4	75.9±3.1*	69.3±3.4
11-18 days	99.5±0.3	100±0	100±0	100±0	100±0

Note: * – P<0.05 in comparison to the control group.

Table 5. The evaluation of the effectiveness of wound epithelization in animals of various experimental groups

Time frame for study, days	Control, n=7	Aloe juice, 100 mcL per wound, n=8	Schaftoside 0.1. uG/mL, 100 mcL per wound, n=8	Schaftoside 1.5 uG/mL, 100 mcL per wound, n=9	Schaftoside 3.0 uG/mL, 100 mcL per wound, n=10
The proportion of animals with complete epithelization of the defect site, %					
21 days	0	25*	37.5*	33.3*	50*
The proportion of animals with thin epithelium at the site of the defect, %					
21 days	85.7	50	25*	33.3*	10*#

Note: * – P<0.05 in comparison to the control group; # – P<0.05 in comparison to the group where aloe juice was applied.

Under the influence of schaftoside at a concentration of 3.0 uG/mL, 50% of mice had complete epithelialization. Only 10% of animals had the defect covered with thin epithelium, which was significantly thinner than in the control group and the group where aloe juice (the comparison drug) was applied. Schaftoside at concentrations of 0.1 uG/mL and 1.5 uG/mL compared to the control parameters also significantly improved the regenerate quality, but in comparison to aloe juice, the structure of the skin regenerate was observed to tend to improve.

Conclusione

Thus, the results of the study conducted on the model of a plane skin wound allowed establishing that the proposed drug, the compound schaftoside – apigenin-6-C-β-D glucopyranosyl 8-C-α-L arabinopyranoside ($C_{26}H_{28}O_{14}$) from *Lychnis chalcedonica* L., at concentrations of 0.1 uG/mL, 1.5 uG/mL, 3.0 uG/mL when applied externally (topically), contributes to a significant reduction in the size of plane skin wounds, comparable to the action of aloe juice (the comparison drug). The wound healing effect is more pronounced at the first, second, and third weeks of the healing process, i.e. at the stage of inflammation, proliferation, and activation of the repair process, if the most objective classification, which reflects the most significant characteristics of the wound process, is applied. Under the influence of schaftoside at a concentration of 3.0 uG/mL, a more complete epithelialization was recorded than in the group where the comparison drug (aloe juice) was applied.

Conflict of interests

The authors do not declare a conflict of interests.

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