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The effect of the gel with tricolor violet extract on the activity of the antioxidant defense system in rats with a model of paro-dontitis

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Abstract: The authors investigated the antioxidant properties of the gel with tricolor violet extract when used in rats with an experimental parodontitis model. To simulate periodontal pathology, white laboratory rats were given a solution of ethylenediaminetetraacetic acid (2%) daily with drinking water and three times a week; the drug "Warfarin Orion" was administered per os for 30 days. Animals were randomly divided into four equal groups of 10 each. Group 1 - intact rats; group 2 - rats with a model of parodontitis; group 3 - rats with a model and applications on the mucous membrane of the alveolar process gel "Placebo". Group 4 - rats with a parodontitis model and applications on the mucous membrane of the alveolar process of the gel with the violet extract. In periodontal tissues and blood serum, we studied the level of inflammation markers - malondialdehyde (MDA) and diene conjugation. The state of the antioxidant defense system (AODS) was also assessed by the activity of glutathione peroxidase (GP), glutathione reductase (GR), glucose-6-phosphate dehydrogenase (G-6-PD), superoxide dismutase (SOD), and catalase. The parodontitis model in rats of the 2nd group was characterized by the development of inflammatory processes in periodontal tissues and blood, which is confirmed by changes in the pro- and antioxidant protection system. In rats of the 4th group, the content of MDA was restored in periodontal tissues. The state of the AOP system was normalized (decrease in the activity of SOD and catalase to the values of group 1), the tension in the glutathione-antioxidant defense system disappeared (the activity of GP decreased, and the activity of GR and G-6-PDH increased to the level control). In the blood serum, the content of MDA significantly reduced, and the level of DC remained higher than in group 1.In contrast, stabilization of the activity of marker enzymes of glutathione-antioxidant protection in blood serum (GP, GR, G-6-PDH) was noted with significant activation of the activity of SOD and catalase, with stabilization of SOD and catalase.

Conclusion. The periodontal protective effectiveness of the gel with tricolor violet was established, as evidenced by the restoration of the state of protective antioxidant systems and the inhibition of lipid peroxidation processes both directly in the periodontal tissues and at the system level.

Keywords: experimental parodontitis, lipid peroxidation, antioxidant protection, gel with tricolor violet.

Introduction

The pathogenesis of periodontal diseases is multifaceted; studies have identified the primary mechanisms for developing this pathology [1, 2]. In recent years, a lot of material has been accumulated on the role of changes in local immune and coagulation potential and changes in the system of lipid peroxidation absorption - antioxidant protection (LPO/AOP) in the genesis of periodontal pathology [3, 4, 5]. One of the biochemical links of the initial pathological changes in periodontal tissues during the formation of periodontal disease is the activation of free radical oxidation [6]. Changes in lipid peroxidation intensity are the cell`s response to any unfavorable influence of external and internal factors. LPO directly transfers oxygen to the substrate by forming peroxides, ketones, and aldehydes, and a distinctive feature of this process is a chain, self-indicating character [7, 8]. In chronic aggressive parodontitis, there is a local increase in reactive oxygen species (ROS) production. These molecules can cause destroy periodontal tissues by stimulating osteoclastic bone resorption [9]. Various types of antioxidants protect the body from excess ROS, which maintains the LPO/AOD balance in the body. Glutathione is a vital redox regulator in the gingival sulcus fluid, so maintaining a stable ratio of reduced to oxidized glutathione is essential to ensure periodontal health [10].

Many medications have been proposed to treat periodontal diseases; however, they are not always effective, as they can cause side effects [11]. Relevant for dentistry is the use of non-drug preparations, for example, natural remedies that have a pronounced therapeutic effect and practically no adverse side effects [12, 13]. The top link in the algorithm for treating inflammatory periodontal diseases is a local effect, so, today using a gel composition is considered promising [14, 15].

We have developed the "Violet" gel, which includes a complex of biologically active substances of plant origin obtained from the tricolor violet. The use of violet tricolor as a medicinal plant has a long history. It is reported that extracts obtained from tricolor violet have a pronounced anti-inflammatory effect due to the presence of biologically active cyclotides that inhibit the proliferation of activated lymphocytes due to a decrease in the secretion of IL-2 cytokines [16]. The dominant flavonoid compound of tricolor violet is rutin, a quercetin glycoside, which belongs to the group of angioprotectors and microcirculation correctors; besides, it is one of the best natural antioxidants [17, 18]. Rutin has a variety of therapeutic activities: antibacterial, antiprotozoal, anti-inflammatory, antiallergic, cytoprotective, vasoactive, hypolipidemic, antiplatelet, antispasmodic, and antihypertensive [19, 20].

Given the above, the work aim is to study the antioxidant properties of the gel for the oral cavity with violet extract in a parodontitis model in rats.

Materials and methods.

Experimental studies were carried out on 40 white laboratory rats weighing 160-180 g, in the conditions of the vivarium of the State Establishment "Institute of Dentistry and Maxillofacial Surgery of the Academy of Medical Sciences", Odesa. Experimental studies were carried out in accordance with the Law of Ukraine “On the Protection of Animals from Cruelty” and the national “General Ethical Principles of Experiments on Animals”, which are consistent with the provisions of the “European convention for the protection of vertebrate animals used for experimental and other scientific purposes (1986). The study was approved by the Animal Research Ethics Committee. All rats were allowed to acclimatise to the housing conditions for one week prior to the start of the study. Animals were kept on a 12-hour light/dark cycle at 20 ± 5°C and 20–30% humidity in a temperature-controlled room. Five rats were placed in each cage for the study. Experimental modeling of periodontal pathology in rats was carried out as follows: animals were given a 2% solution of

ethylenediaminetetraacetic acid (EDTA) daily with drinking water and three times a week were injected per os with the drug "Warfarin-Orion" by Orion Corporation, Finland (Finland) mg / kg (in terms of the active substance warfarin sodium - 0.01 mg / kg) for 30 days. The rats were divided into 4 groups of 10 animals each. Group 1 - intact animals, group 2 - animals with a parodontitis model, group 3 - animals with a parodontitis model, which, starting from the 7th day, daily, for 3 weeks, applied gel "Placebo" on the gum mucosa, group 4 - animals with a parodontitis model, which, starting from 7 days daily, for 3 weeks, were applied to the mucous membrane of the gums with a gel with an extract of tricolor violet.

In blood serum and periodontal tissues, we studied the level of inflammation markers - malondialdehyde (MDA) [21] and diene conjugation (DC) [21]. MDA was determined spectrophotometrically. The principle of the method is that at high temperatures in an acidic medium, MDA reacts with 2-thiobarbituric acid, reproducing a colored trimethine complex with an absorption maximum of 532 nm. HA was determined by spectrophotometry. The principle of the method is to mix blood plasma with a heptane-isopropanol mixture, followed by separation of the heptane phase and determination of the optimal density of the mixture at 232 nm.

The state of the antioxidant defense system (ADS) was also assessed by the activity of superoxide dismutase (SOD), catalase (KAT), glutathione peroxidase (GP), glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G-6-PD).

The activity of SOD was determined by spectrophotometers. The method is based on determining the degree of inhibition under the influence of SOD of the biological substrate of the nitro blue tetrazolium reduction reaction by superoxide radicals. The generation of the latter is carried out in the NADH - phenosine methosulfate system [21].

Catalase activity was determined using spectrophotometry. The method`s principle is based on the ability of hydrogen peroxide to form a stable colored complex with molybdenum salts [21].

Glutathione peroxidase activity was determined by spectrophotometry. The method is based on the determined amount of reduced glutathione that is not used in the course of the glutathione peroxidase reaction when this thiol is added to a medium containing tert-butyl hydroperoxide as a substrate [21].

Glutathione reductase activity was determined by spectrophotometry. The principle of the method: the decrease in NADPH2 content in the test sample was determined spectrophotometrically at a wavelength of 340 nm (absorption maximum of the reduced coenzyme) [21].

The G6PD activity was determined in the basis of NADPH production at 340 nm and 37^{o}C by kinetic method. [22].
All data were processed using the statistical package Statistica 10.0 (Statsoft/Dell, Tulsa, OK, USA). The descriptive statistics of the data in tables include mean ± standard error of the mean (SEM) or mean ± standard deviation. Significance was assessed by using the one-way ANOVA followed by t-test. Values were considered statistically significant when P value is less than 0.05.

Results

A vital marker indicator of the activity of metabolic processes occurring in different body tissues is the intensity of lipid peroxidation. Therefore, the study of pro- and protective antioxidant systems that balance between the formation and metabolism of reactive oxygen species in cells is an essential step in studing the pathogenetic mechanisms of the

development of various types of pathology, including periodontal diseases. The conducted studies showed that with the development of the parodontitis model in animals of all experimental groups, the level of HA significantly increases (the initial stage of LPO). In the 2nd group, the increase was 92%; in the 3rd - 65%; and in the 4th group - 58% compared with the 1st control group of intact rats (Table 1). At the same time, the level of MDA significantly increased by 21% and 29% in animals of the 2nd and 3rd groups. In the 4th group, this indicator had only a weakly expressed tendency to increase ($p > 0.05$).

The study of the state of AOD determined that the activity of the SOD enzyme significantly increased in all groups by 25, 30, and 33%, which indicates the intensification of the processes of blocking reactive oxygen species in the body. At the same time, an increase in the activity of the catalase enzyme was observed - by 19%, 19%, and 22% (p 0.05). However, a specific ratio of SOD and catalase activity is important for the vital activity of cells since an increase in SOD without a corresponding activation of catalase is cytotoxic. When evaluating the SOD/CAT ratio, it was found that this indicator in the 2nd and 3rd groups was 11% and 9% higher than the control level. In the 4th group, it does not differ from the control group.

Table 1. Study of the state of the pro- and antioxidant system in the blood serum of rats, (M ± m)

Indicators	1st group n=10	2nd group n=10	3rd group n=10	4th group n=10
MDA, μmol/ml	0,37 ± 0,02	0,48 ± 0,02*	0,47 ± 0,03*	0,41 ± 0,01
DC, RU/ml	1,35 ± 0,10	2,60 ± 0,37*	2,24 ± 0,19*	2,14 ± 0,18*
SOD, U/ml × min	188,1 ± 10,4	235,9 ± 14,3*	245,0 ± 10,5*	250,2 ± 12,3
CAT, RU/ ml × min	0,68 ± 0,04	0,81 ± 0,03*	0,81 ± 0,04*	0,83 ± 0,04*
SOD/CAT	277	309	303	284

Note: * - significant changes in indicators compared with the 1st group ($p<0.05$).

To obtain complete information about the state of the ATC system, we studied of the link in the state of glutathione-antioxidant protection (Table 2). Glutathione peroxidase (GP) is one of the most important antioxidant enzymes since it detoxifies not only hydrogen peroxide but also organic peroxide without forming radical products. At the same time, its localization in cellular structures coincides with the localization of SOD. It acts more efficiently concerning low levels of hydrogen peroxide than catalase (because it has a lower value of the Michaelis constant Km and, accordingly, a higher affinity of H2O2). According to the results obtained, it was determined that GP activity was significantly reduced only in the 2nd and 3rd groups - by 21% and 25%, respectively, while in the 4th group of animals, it resumed (Table 2).

It is known that the main function of glutathione reductase is to maintain the pool of reduced glutathione involved in protecting of cellular structures from oxidative damage. Therefore, GR is a limiting link in the GP-GR system. It was found that in animals of the 2nd and 3rd groups, there was a significant decrease in OR activity by -25% and 18% and

in the 2nd group, a significant reduction in the activity of glucose-6-phosphate dehydrogenase (G-6-PDH) – by 26%. In the 4th group of animals, this indicator also did not have significant differences compared with the 1st control group.

Table 2. Study of the state of the glutathione-antioxidant system in the blood serum of rats, (M ± m)

Indicators	1st group n=10	2nd group n=10	3rd group n=10	4th group n=10
GP, μmol oxid. glutathione/ml×min	4,15 ± 0,30	3,30 ± 0,23*	3,13 ± 0,29*	4,39 ± 0,24
GR, μmol $NADPH_2$/ml × min	6,57 ± 0,30	4,93 ± 0,39*	5,38 ± 0,33*	6,78 ± 0,52
G6PDH, μmol $NADPH_2$/ml × min	1,89 ± 0,12	1,38 ± 0,13*	1,64 ± 0,18	1,64 ± 0,20

Note: * - significant changes in indicators compared with the 1st group ($p<0.05$).

An important informative indicator of the development of the pathological process and the effectiveness of the use of a therapeutic agent (gel) is the state of the LPO/AOP system directly in periodontal tissues (Table 3). The parodontitis model in animals of the 2nd group is characterized by a significant increase in the content of MDA by 24%, with simultaneous activation of SOD and catalase (their activity increased by 39% and 100%, respectively). In 3rd group, which applied the gel "Placebo", this system had a similar activation. The content of MDA increased by 19% with a simultaneous increase in the activity of SOD and catalase by 28% and 65%.; that is, no positive changes were observed.

Table 3. Study of the state of the pro- and antioxidant system in rats in periodontal tissues, (M ± m)

Indicators	1st group n=10	2nd group n=10	3rd group n=10	4th group n=10
MDA, μmol/g of tissue	42,00±1,70	52,10±1,70*	50,10±3,30*	45,10±2,70
SOD, un/g of protein × min	126,1±10,0	176,6±17,1*	161,1±11,8*	139,9±12,7
CAT, un/g of protein × min	0,17±0,01	0,34±0,02*	0,28±0,02*	0,21±0,01*

Note: * - significant changes in indicators compared with the 1st group ($p<0.05$).

In group 4 rats, the following changes were observed: restoration of the MDA content (prevention of LPO activation) and normalization of the state of the AOD system, as evidenced by the restoration of SOD activity and a significant decrease in catalase activity. In rats of groups 2 and 3, signs of tension were also found in the glutathione-antioxidant defense system (Table 4).

Table 4. Study of the state of the glutathione-antioxidant system in rats in periodontal tissues, (M ± m)

Indicators	1st group n=10	2nd group n=10	3rd group n=10	4th group n=10
GP, μmol oxid. glutathione/mg protein × min.	1,36±0,10	2,09±0,18*	2,01±0,19*	1,19±0,07
GR, μmol $NADPH_2$/mg protein × min	2,10±0,11	1,56±0,16*	1,71±0,14*	2,35±0,24
G6PDH, μmol $NADPH_2$/mg protein × min	4,77±0,27	3,09±0,41*	3,77±0,27*	4,85±0,23

Note: * - significant changes in indicators compared with the 1st group ($p<0.05$).

The activity of the key GR enzyme significantly decreased by 26% and 19%, and the activity of the supplier of reduced equivalents (G-6-PDG) decreased by 36% and 21%, respectively ($p<0.05$). At the same time, a significant compensatory increase in GP activity was observed - by 53% in group 2 and by 48% in group 3, due to an increase in the consumption of the reduced glutathione pool. That is, the balance of reduced/oxidized glutathione in the tissues was disturbed, which indicates the depletion of the reserves of the antioxidant defense system. When using the therapeutic gel in animals of the 4th group, the lack of resources of the antioxidant defense system was not observed.

Discussion.

The intensification of lipid peroxidation processes in modeling parodontitis in animals was characterized by an increase in the level of DC and MDA in the blood serum by 32.6 and 92% ($p<0.01$) relative to the control and proceeded against the background of an imbalance in the work of the antioxidant defense system. Inhibition of the activity of the enzymes GP, GR, and G-6-PD by more than 26.0% ($p<0.05$) and a compensatory increase in catalase activity by 19.1% ($p<0.05$) was revealed. At the same time, the SOD/CAT ratio was 1.12–1.24 times higher than the control, which indicates an increase in the formation of reactive oxygen species and a disruption in the balanced operation of this system, which can lead to the development of cytotoxic effects in tissues and an increase in the severity of hypoxic conditions. Similar changes were observed in periodontal tissues. Some authors obtained a similar effect of imbalance in the AOP system against the background of significant LPO activation when reproducing the parodontitis model [23]. Changes in the activity of ADS enzymes in blood and tissues are essential indicators of the body's nonspecific resistance in various types of pathology. They can be used for diagnostic and prognostic purposes [24, 25]. The system of reduced glutathione – oxidized glutathione – is considered a buffer that protects cell membranes and other structures from oxidants. A decrease in the content of reduced glutathione as a result of its oxidation, disruption of its synthesis, an increase in the rate of its decay, or due to a change in the rate of enzyme systems that regulates its level in the cell can lead to the development of pathological processes [26]. The obtained research data correlate with the previously obtained results on modeling experimental parodontitis [27].

The study of the periodontal protective properties of the "Placebo" gel did not reveal any positive changes in the condition of the animals in terms of biochemical parameters concerning the animals of the second group (parodontitis model). At the same time, significant changes in all the studied parameters relative to the control group remained,

both at the systemic level and local (in periodontal tissues): the state of pro- and antioxidant systems in both serum and periodontal tissues maintained a pronounced imbalance throughout the experiment - an increase in DC and MDA by more than 65.4 and 20.0% ($p<0.05$), a reduction in the activity of the glutathione-antioxidant system (in terms of GP, GR, G-6-PD - a decrease by 1.2-1.3 times ($p< 0.05$)) and a compensatory increase in catalase activity by 1.4 times ($p<0.05$).

The study of the periodontal protective properties of the gel with violet in rats with a parodontitis model showed its effectiveness at the systemic level and in periodontal tissues. This output is confirmed by a significant decrease in the content of MDA by 1.1–1.2 times, while the level of DC remained 1.3–1.6 times higher than in control ($p<0.01$), blood serum (GP, GR, G-6-PDH) with significant activation of SOD and catalase activity by 1.2 times ($p<0.05$) with stabilization of the ratio of SOD and catalase. In periodontal tissues, the balance of LPO/AOP was restored. Similar data are presented in the work of the authors who evaluated the effectiveness of the internal use of acai palm juice (Euterpe oleracea Mart.), which is characterized by a high content of plant antioxidants, in experimental parodontitis in rats [28]. Our data largely coincide with the authors` data on the antioxidant properties of curcumin gel [29]. In their opinion, the high efficiency of the gel is determined to a greater extent by the application method, that is, local action, namely, the gel getting directly into the lesions. Previous work by these authors has established the low efficacy of curcumin when used internally.

Conclusions.

Thus, we found that using a gel with tricolor violet in rats with a parodontitis model has a positive effect on the state of periodontal tissues. This positive effect is due to the normalization of the of lipid peroxidation activity (decrease in the content of malondialdehyde) and the restoration of the activity of enzymes (superoxide dismutase and catalase) and glutathione-antioxidant systems of antiradical protection.

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